VOLUME 95 • JUNE 1958 • NUMBER 6

A.M.A. JOURNAL OF

DISEASES OF CHILDREN

INDEX NUMBER

Metastatic Embryonal Rhabdomyosarcoma in the Growing Skeleton
John Caffey and Dorothy H. Andersen

Relationship of Measles and Distemper
John M. Adams, David T. Imagawa, David L. Chadwick, Emily H. Gates, and Robert A. Siem

Comparison Study: Silver Nitrate and Oxytetracycline in Newborn Eyes
Peter L. Mathieu Jr.

Twisted Hairs (Pili Torti)
Samuel J. Nichamin

Thyroid Function in the Perinatal Period
Donald E. Pickering, Nicholas E. Kontaxis, Ralph C. Benson, and Robert J. Meechan

The Effect of a Corn Oil-Evaporated Milk Mixture on Serum Cholesterol Levels in Infancy
Julius Pomeranze, Alta Goalwin, and Lawrence B. Slobody

Meat in the Diet of Premature Infants
Thomas R. C. Sisson and Lorraine E. Whalen

Gynecomastia and Pseudoprecocious Puberty Following Diethylstilbestrol Exposure
Morris Green

Metaphyseal Dysostosis Resembling Vitamin D-Refractory Rickets
Robert Evans and John Caffey

Coexistent Pregnancy of Unequal Twins
Henry K. Silver and Peter Cunningham

The de Toni-Fanconi Syndrome with Cystinosis
Howard G. Worthen and Robert A. Good

Abstracts from Current Literature

News and Comment

Books

AMERICAN MEDICAL ASSOCIATION PUBLICATION

For Ample Air Right Now!

in Asthma

and other Allergic States

Medihaler-EPI®

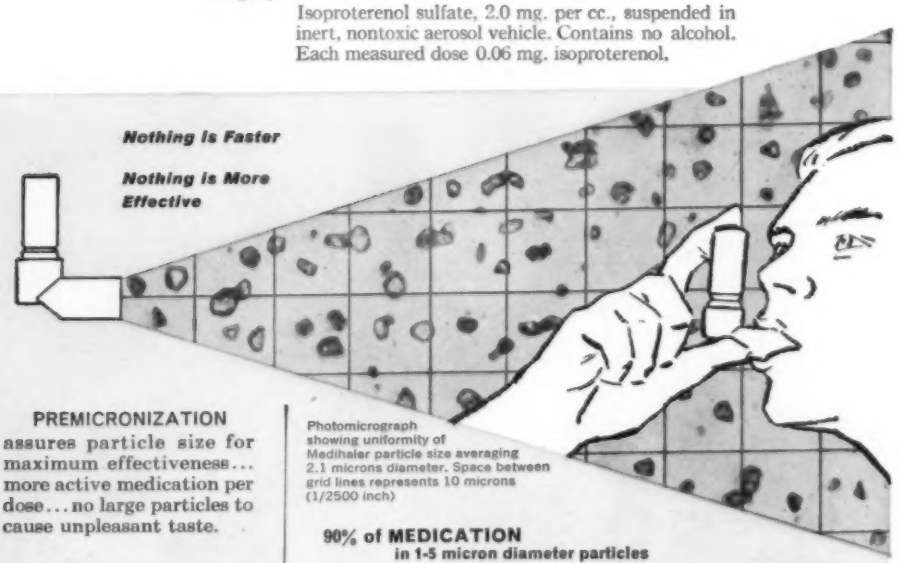
For quick relief of bronchospasm of any origin. More rapid than injected epinephrine in acute allergic attacks.

Epinephrine bitartrate, 7.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose 0.15 mg. epinephrine.

Medihaler-ISO®

Unsurpassed for rapid relief of symptoms of asthma and emphysema.

Isoproterenol sulfate, 2.0 mg. per cc., suspended in inert, nontoxic aerosol vehicle. Contains no alcohol. Each measured dose 0.06 mg. isoproterenol.



PREMICRONIZATION assures particle size for maximum effectiveness... more active medication per dose... no large particles to cause unpleasant taste.

THE MEDIHALER® PRINCIPLE means automatically measured-dose aerosol medications in spill-proof, leakproof, shatter-proof, vest-pocket size dispensers.

Photomicrograph showing uniformity of Medihaler particle size averaging 2.1 microns diameter. Space between grid lines represents 10 microns (1/2500 inch)

90% of MEDICATION
in 1-5 micron diameter particles

99.9% of PARTICLES
in 1-7 micron diameter range

New Improved Premicronized Medihaler suspension
...55 mcg. drug/dose 1-5 microns range

Old type aerosol solution.....	10-12 mcg. drug/dose 1-5 microns range
Squeeze bulb nebulizers.....	2-3 mcg. drug/dose 1-5 microns range

Riker
LOS ANGELES

TABLE OF CONTENTS

VOLUME 95 JUNE 1958 NUMBER 6

ORIGINAL ARTICLES

PAGE

Metastatic Embryonal Rhabdomyosarcoma in the Growing Skeleton
John Caffey, M.D., and Dorothy H. Andersen, M.D., New York 581

Relationship of Measles and Distemper
John M. Adams, M.D.; David T. Imagawa, Ph.D.; David L. Chadwick, M.D.; Emily H. Gates, M.D., and Robert A. Siem, Ph.D., Los Angeles 601

Comparison Study: Silver Nitrate and Oxytetracycline in Newborn Eyes
Peter L. Mathieu Jr., M.D., Providence, R. I. 609

Twisted Hairs (Pili Torti)
Samuel J. Nichamin, M.D., Detroit 612

Thyroid Function in the Perinatal Period
Donald E. Pickering, M.D.; Nicholas E. Kontaxis, M.D.; Ralph C. Benson, M.D., and Robert J. Meechan, M.D., Portland, Ore. .. 616

The Effect of a Corn Oil-Evaporated Milk Mixture on Serum Cholesterol Levels in Infancy
Julius Pomeranze, M.D.; Alta Goalwin, M.D., and Lawrence B. Slobody, M.D., New York 622

Meat in the Diet of Premature Infants
Thomas R. C. Sisson, M.D., and Lorraine E. Whalen, Rochester, N. Y. 626

CASE REPORTS

Gynecomastia and Pseudoprecocious Puberty Following Diethylstilbestrol Exposure
Morris Green, M.D., Indianapolis 637

Metaphyseal Dysostosis Resembling Vitamin D-Refractory Rickets
Robert Evans, M.D., and John Caffey, M.D., New York 640

Coexistent Pregnancy of Unequal Twins
Henry K. Silver, M.D., Denver, and Peter Cunningham, M.D., New Haven, Conn. 649

PROGRESS IN PEDIATRICS

The de Toni-Fanconi Syndrome with Cystinosis
Howard G. Worthen, M.D., and Robert A. Good, Ph.D., M.D., Minneapolis 653

REGULAR DEPARTMENTS

Abstracts from Current Literature 689

News and Comment 703

Books 704

A. M. A.
Journal of Diseases of Children

VOLUME 95 JUNE 1958 NUMBER 6

COPYRIGHT, 1958, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

RICHARD L. DAY, Chief Editor
State University of New York College of Medicine, Downstate Medical Center
450 Clarkson Ave., Brooklyn 3

ROBERT A. ALDRICH, Seattle
RICHARD L. DAY, Brooklyn
ROGER L. J. KENNEDY, Rochester, Minn.
ROBERT B. LAWSON, Miami, Fla.
FRANCIS SCOTT SMYTH, San Francisco
A. A. WEECH, Cincinnati
WARREN E. WHEELER, Columbus, Ohio
JAMES L. WILSON, Ann Arbor, Mich.
WOLF W. ZUELZER, Detroit

ASSOCIATE EDITORS

SYDNEY S. GELLIS, Boston
ROBERT A. GOOD, Minneapolis
ROBERT JACKSON, Columbia, Mo.
VINCENT C. KELLEY, Salt Lake City
C. HENRY KEMPE, Denver
STUART S. STEVENSON, Pittsburgh
HENRY WORK, Los Angeles

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

SUBSCRIPTION RATES

Price per annum in advance, including postage: Domestic, $12.00. Canadian, $12.50. Foreign, $13.50. Price to students, interns, and residents, $7.00 in U. S. & possessions.

Single copies of this and previous calendar year, $1.25.

Back issues older than two years are available through Walter J. Johnson, Inc., 111 Fifth Avenue, New York 3. Future reprints of back issues will be available through Johnson Reprint Corporation, 111 Fifth Avenue, New York 3.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

for the orthalimentation of infants

ORTHALIMENTATION*=*Correct Nourishment–in quantity, quality and balance***

In a period when medical progress has made *hypo*alimentation an academic formulation rather than a real problem, the interest of those concerned with correct infant feeding is directed more toward the excesses of *hyper*alimentation.

The clinical objective of orthalimentation is to achieve a balance between either extreme by the introduction of correct nutrients into the infant's alimentary tract. In practical terms for artificial infant feeding, this means a feeding which, in both content and clinical benefits, is the closest possible equivalent to human milk.

SIMILAC meets these clinical criteria in content and balance of protein, fat, carbohydrate and vitamins, and in minimizing complications in infant feeding.

SIMILAC®

*ORTH ('Ορθος) ALIMENTATION *is the subject of a monograph issued by Ross Laboratories, which is available to you on request.*

ROSS LABORATORIES, *Columbus 16, Ohio*

RESEARCH · SERVICE · NUTRITION

Instructions to Contributors

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor. Articles are accepted for publication on condition that they are contributed solely to this journal.

An original typescript of an article, with one carbon copy, should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. Another carbon copy should be retained by the author.

The main title of an article may not contain more than eighty characters and spaces; a subtitle may be of any length.

The author's name should be accompanied by the highest earned academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

If it is necessary to publish a recognizable photograph of a person, the author should notify the publisher that permission to publish has been obtained from the subject himself if an adult, or from the parents or guardian if a child. An illustration that has been published in another publication should be accompanied by a statement that permission for reproduction has been obtained from the author and the original publisher.

Oversized original illustrations should be photographed and a print on glossy paper submitted. Prints of a bluish tinge should be avoided. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author. The author should submit duplicate prints of roentgenograms and photomicrographs with the essential parts that are to be emphasized circled, as a guide to the photoengraver.

Charts and drawings should be in black ink on hard, white paper. Lettering should be large enough, uniform, and sharp enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, and an abbreviated title of the article, and plainly indicating the top. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be limited to those used by the author in preparation of the article. They should be typed on a special page at the end of the manuscript. The citation should include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. References to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

MEYENBERG GOAT MILK...

A FIRST CHOICE FOR INFANTS ALLERGIC TO COWS MILK...

FOR INFANTS allergic to cow's milk, Meyenberg Goat Milk is a medication of choice. Since the offending antigen in cow's milk is usually lactalbumin, a species-specific protein, goat milk has frequently proven a practical and successful substitute for cow's milk. Goat milk does not deprive the infant of the important values of milk.

Recent clinical findings indicate that the promiscuous use of milk-free substitutes is not without deleterious effects. Sensitivity to soy protein with cross sensitization to other legumes has been demonstrated. In addition, gastrointestinal disturbances with abnormal stools, diarrhea, sore buttocks, cramping and occasionally vomiting, have been reported following the ingestion of soybean containing preparations.***

In light of this evidence, for infants allergic to cow's milk, prescribe Meyenberg Goat Milk FIRST. It is nutritionally equal to cow's milk in protein, carbohydrates and fat . . . It contains no crude fibers or other extraneous material which may cause digestive upset. Meyenberg Goat Milk is rich in animal protein and accessory growth factors. Most important of all . . . it is not a milk substitute, but milk itself.

Evaporated in 14 fluid oz. cans, powdered in 14 oz. cans.

Write for a full can size sample to:

JACKSON-MITCHELL *Pharmaceuticals, Inc.*

10401-A Virginia Avenue, Culver City, California. SINCE 1934

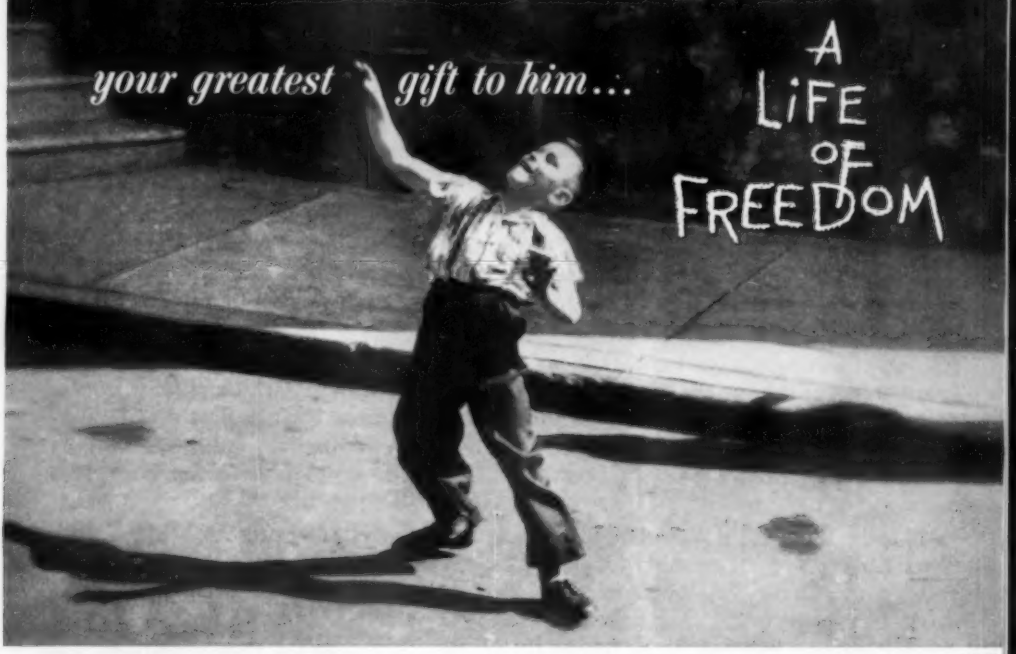
* Fries, J. H., Milk Allergy-Diagnostic Aspects and the Role of Milk Substitutes, J.A.M.A., Nov. 23, 1957.

** Ibid.

Write for a free reprint of this article.

Dim hopes and grave doubts need no longer be a part of the epileptic's life. Today's clinical advances, coupled with your increasing knowledge of therapy, may give the epileptic what he dared not hope for in the past: **a normal life.** These five distinguished anticonvulsants can help you treat the epileptic—from childhood on through his adult years. They will help you give him the safety, comfort and security that comes only with a seizure-free life.

Abbott



800107

ANTICONVULSANTS BY ABBOTT

PEGANONE®
(Ethotoin, Abbott)

Newest of Abbott's anticonvulsants . . . a new hydantoin of exceptionally low toxicity for grand mal *and psychomotor seizures.*

PHENURONE®
(Phenacemide, Abbott)

Used with discretion, will often prove successful where all other therapy fails in treating psychomotor, grand mal, petit mal *and mixed seizures.*

GEMONIL®
(Metharbital, Abbott)

An effective drug with low toxicity for treating grand mal, petit mal, *myoclonic and mixed seizures symptomatic of organic brain damage.*

TRIDIONE®
(Trimethadione, Abbott)
PARADIONE®
(Paramethadione, Abbott)

Two eminently successful anticonvulsants for symptomatic control of petit mal, *myoclonic and akinetic seizures... Tridione will often work where Paradione won't and* vice versa.

Little Boy Blue blows his horn for delicious apple-flavored

ABDEC® DROPS

comprehensive multivitamin formula

NOW WITH VITAMIN B_{12} AND WITH

Each 0.6 cc. of ABDEC DROPS now supplies:

Vitamin A	5,000 units (1.5 mg.)
Vitamin D	1,000 units (25 mcg.)
Vitamin C (ascorbic acid)	50 mg.
Vitamin B_1 (thiamine hydrochloride)	1 mg.
Vitamin B_2 (G) (riboflavin)	1.2 mg.
Vitamin B_6 (pyridoxine hydrochloride)	1 mg.
Pantothenic acid (as the sodium salt)	5 mg.
Nicotinamide	10 mg.
Vitamin B_{12}	2 mcg.

Supplied in bottles of 15 and of 50 cc. with calibrated plastic droppers.

Nicotinamide doubled
Pantothenic acid more than doubled
Riboflavin tripled
for better-than-ever nutritional support

- stable—needs no refrigeration
- hypoallergenic
- easy to give in foods or fluids or directly on the tongue

PARKE, DAVIS & COMPANY · DETROIT 32, MICHIGAN

for Strategic Nutrition

in Pediatrics

Whether meals must be planned for
weight-losing, weight-gaining,
or just for normal day-to-day
growth-promoting nutrition . . .

Enriched Bread

with its growth-applicable protein, available energy, B vitamins, iron and calcium, has a well-justified place in every meal.

Because it is also an excellent vehicle for other foods, it fills an especially strategic position at snacktime.

AMERICAN BAKERS ASSOCIATION

20 North Wacker Drive Chicago 6, Illinois

now

antiemetic and full-range tranquilizer benefits extended to all age groups particularly children

Trilafon® Syrup

perphenazine 2 mg./tsp.

PRESCRIBE IT IN CHILDREN FOR

- nausea and vomiting
- behavioral problems
- mild, moderate and severe emotional and mental disorders

PRESCRIBE IT IN ADULTS FOR

- elderly patients who prefer liquid medication

PRESCRIBE IT BECAUSE

- behavioral and antiemetic potency are unexcelled
- mental acuity is usually unimpaired
- significant hypotension is absent
- agranulocytosis has not been reported

For dosage in children and adults, precautions and contraindications, consult Schering literature.

Packaging: TRILAFON Syrup, 2 mg. in each teaspoon (5 cc.), 4 oz. bottle.

outmoding older concepts

Schering

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

TR-J-1030

Doctor, your dietary decision can build Blue Ribbon babies

The baby who wins the blue ribbon is the one whose doctor—no one else—determines its exact nutritional needs.

GET YOUR BABIES OFF TO A STRONG START WITH...

Varamel®

A scientifically formulated evaporated milk product prepared exclusively from Grade A Milk

Happy Lynn Patricia, aglow with health, is a Blue Ribbon winner, pride of her doctor who selected VARAMEL to get her off to a strong start.

VARAMEL BUILDS BLUE RIBBON BABIES

- Made from milk of outstanding purity.
- Scientifically formulated for optimum nutrition.
- Helps prevent colic.[1] Butterfat replaced by easily digested vegetable oils.
- Twice homogenized for better digestion and absorption.
- Permits prescribing carbohydrate of choice. No sugar added.
- Provides adequate amounts of all known essential vitamins plus much-needed iron.
- Helps doctor control infant feeding longer. Advertised to the medical profession only. Available in drug stores.
- Economical to use— eliminates need for additional vitamins and iron.

Approximate Analysis

Protein	4.9%	Calcium	0.19%
Carbohydrate	8.3	Phosphorus	0.15
Fat	5.8	Iron	0.0016
Ash	1.2	Moisture	79.9

32 Calories per fl. oz.

Average dilution—equal parts of Varamel and water plus sufficient carbohydrate to make 20 calories per fluid ounce.

1. Braslow, L.: Clinical Approach to Infantile Colic. J. Pediat. 50: 196-206, 1957. (Reprint sent on request.)

Other products–Baker's Modified Milk—a completely prepared formula in liquid and powder form.

The Baker Laboratories, Inc. • Cleveland 3, Ohio

Milk Products Exclusively for the Medical Profession

"Doctor, Tommy's thrown up three times!"

'Thorazine' promptly controls the vomiting of acute gastroenteritis. Even when vomiting has been protracted, the profound antiemetic effect of 'Thorazine' helps to restore food intake and hydration, thereby eliminating the need for parenteral fluids.

THORAZINE*

Especially for pediatric use:
'Thorazine' Syrup and 'Thorazine' Suppositories

Also available in tablets, ampuls, Spansule† capsules and the new 10 cc. (25 mg./cc.) multiple dose vials.

Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off. for chlorpromazine, S.K.F. †T.M. Reg. U.S. Pat. Off. for sustained release capsules, S.K.F.

Isolation with accessibility: The infant is protected from nursery air by a spacious, transparent hood. Four iris-diaphragm ports and one hinged port provide complete accessibility.

the **Isolette®** infant incubator offers

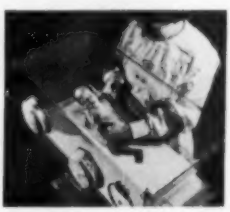
Greater Protection for the Premature

The ISOLETTE, only "completely air-conditioned" infant incubator described and illustrated in the new 2nd edition of *"Premature Infants,"* may serve also as "an isolation unit in addition to maintaining optimal environmental conditions, and is particularly useful in caring for the smallest infants." Dunham, E. C.: *Premature Infants,* 2nd Ed., Hoeber-Harper, New York, 1955.

Moreover, "The ISOLETTE® is probably the greatest single aid available in the surgical care of the tiny infant . . . it provides well-regulated warmth and humidity and economical oxygen concentrations in a convenient working area for nurse and doctor . . . unsurpassed visibility . . . and convenience of handling . . . The isolation of the patient from his neighbors and from the contaminated or ailing doctor or nurse is an additional safeguard. Intravenous cutdowns, weighings, spinal taps and other procedures are all possible within its protective shell." Lynn, H. B.: POSTGRAD. MED., 22:493, Nov. 1957.

Individually air-conditioned, the ISOLETTE® continually draws in fresh air from outside the hospital, protecting the infant from air-borne nursery pathogens, even when iris ports are open.

Positive humidity control with a simple valve. Constant, controlled recirculation of moist, fresh air maintains humidity at desired optimal level, as high as 85% to 100% —without need for additional heat.



Precise temperature control within a tolerance of 1°F., with device for cooling as well as heating, and **automatic alarm** should outside factors cause overheating.

The Isolette®

Fresh-air-flow infant incubator by AIR-SHIELDS, INC.

Phone collect, OSborne 5-5200, Hatboro, Pa., and order with 30-day return privilege.
IN CANADA: AIR SHIELDS (CANADA) LTD., 8 Ripley Avenue, Toronto 3, Ont. (Roger 6-5444)

A.M.A JOURNAL OF
DISEASES OF CHILDREN

Metastatic Embryonal Rhabdomyosarcoma in the Growing Skeleton

Clinical, Radiographic, and Microscopic Features

JOHN CAFFEY, M.D., and DOROTHY H. ANDERSEN, M.D., New York

In 1946 Stout published his classical paper[1] on rhabdomyosarcoma of skeletal muscles, which established, for the first time, the microscopic characteristics of sarcomas of skeletal muscles in the absence of demonstrable cross striations. Stobbe and Dargeon[3] pointed out, in 1950, that the embryonic type of rhabdomyosarcoma of the head and neck in children resembled neuroblastoma and lymphosarcoma. They reported 15 patients with a mean age of 6½ years but who varied in age from 16 months to 16 years; 13 of their patients were 12 years old or younger. In these cases limited to the head and neck, the primary rhabdomyosarcomas developed in orbital, facial, and cervical muscles. The authors state that clinically these tumors were rarely diagnosed early and were often misdiagnosed microscopically. Distant metastases occurred in several sites in 6 of 15 cases: lungs in 4 cases, pleuras in 3 cases, lymph nodes in 3, vertebral column in 2, and pelvis, femurs, uterus, pancreas, thyroid, and brain in 1 each. Although roentgen examination was utilized in the identification of metastases, the radiographic changes of the skeletal lesions are not described. Pack,[5] in a description of a large group of rhabdomyosarcomas, concluded that pulmonary metastases are the most frequent but was surprised at the inconsistency of metastases. In his cases the primary tumors were widely scattered in muscles of the arms, shoulders, legs, thigh, buttocks, groin, chest, back, and abdominal wall. He mentions that, in cases with generalized metastases, the spine is sometimes secondarily involved and also the regional lymph nodes.

In a detailed clinicopathological study of 39 cases of rhabdomyosarcoma, Horn and Enterline[4] classified 13 cases as embryonal in type. These patients varied in age from birth to 23 years; nine were 12 years old or younger. Seven of the primary tumors were in the head and neck in this group, and five of these were located in the orbit; four were in the urogenital tract, and only two were located in muscles in the extremities. Skeletal metastases were located in the spine, long bones, and skull. In only one case were there generalized metastases in the skeleton. The radiographic features of the skeletal metastases were not described. Horn and Enterline also found metastases in the lungs in five cases and in lymph nodes, regional and generalized, in three cases.

Five children are the subject of this report, all of whom had primary malignant tumors located in muscles and presenting

Submitted for publication Feb. 21, 1958.

From the Departments of Pediatrics, Radiology, and Pathology, College of Physicians and Surgeons, Columbia University, and the Babies Hospital.

the microscopic picture of embryonal rhabdomyosarcoma. All the children had scattered metastases in the skeleton which were identified radiographically. The radiographic features of skeletal embryonal rhabdomyosarcoma have not been previously recorded, so far as we know.

Report of Cases

CASE 1.—A Negro girl 32 months of age had been well until her 26th month, when a painless swelling first appeared in the left scapular region. The swelling increased rapidly in size but remained painless. During her 31st month a piece of the swelling was excised, and the parents believed that the findings indicated that their daughter had a "tumor." During the first five months of the swelling the patient was apparently healthy, with normal appetite, nutrition, and activity, but during the last month, the sixth month of the swelling, she became dyspneic, refused to eat, and was inactive. The parents had not detected fever.

Physical findings during her 32d month, 6 months after the first detection of the tumor: Nutrition was surprisingly good in view of the size and age of the thoracic tumor; she weighed 16.3 kg. She breathed with difficulty and was apprehensive of being moved or touched. A huge lobulated swelling extended from the occiput to midthoracic levels on the left side and forward over the left clavicle and into the neck in the submandibular region (Fig. 1A). This great mass of tissue was firm but not overwarm, was apparently painless, and was not tender. The overlying skin was intact save for a biopsy wound which was completely healed. Rotation and extension of the head were limited, but movements at the left shoulder were surprisingly good. The trachea was displaced to the right by the tumor, which had grown into the neck from the left; this tracheal displacement and compression appeared to be the principal cause of dyspnea.

Coarse rales were heard in both sides of the chest. Resonance was unimpaired except in the site of the tumor. Heart signs were faint, but rhythm was normal. Spleen, liver, and kidneys were normal to palpation, and there were no abnormal masses in the abdomen or pelvis. External genitalia were normal. Facial weakness indicated palsy of the left seventh nerve; there were no other neurological deficits.

In roentgenograms of the skeleton (Figs. 1B and 1C), multiple destructive foci were present in metaphyses of long bones and in the right ilium just above the acetabulum. The lateral cortical wall of the right femur was slightly thickened. Findings were normal in the skull, spine, and bones of the hands and feet. Patches of increased density in both lungs resembled pneumonia more than neoplastic foci. The bones of the thorax underlying the tumor were normal radiographically.

Fig. 1A (Case 1).—Photograph of primary thoracic tumor in lateral and dorsal aspect, 6 months after its first appearance in a girl 32 months of age. The healed wound above the clavicle is the site of earlier biopsy.

Fig 1B (Case 1).—Deep terminal transverse bands of irregular density in the metaphyses at the knees. The edges of the ossification centers are smooth, in contrast. Similar but less-marked changes were present in the metaphyses in the arms. Round bones and tubular bones in the hands and feet were not affected.

Laboratory findings: Hemoglobin, 11.5 gm. per 100 cc.; WBC, 13,000 per cubic millimeter, with 59% polymorphonuclear cells, 37% lymphocytes, and 4% monocytes. Urine was normal clinically and cytologically.

A biopsy specimen from a left cervical lymph node was filled with neoplastic cells, most of which were pleomorphic and characteristic of embryonal rhabdomyosarcoma (Figs. 1D and 1E). The tumor showed a fairly close network of broad

Fig. 1C (Case 1).—Irregular marginal destruction of the lateral edge of right ilium and roof of its acetabulum. Lateral cortical wall of right femur is thickened.

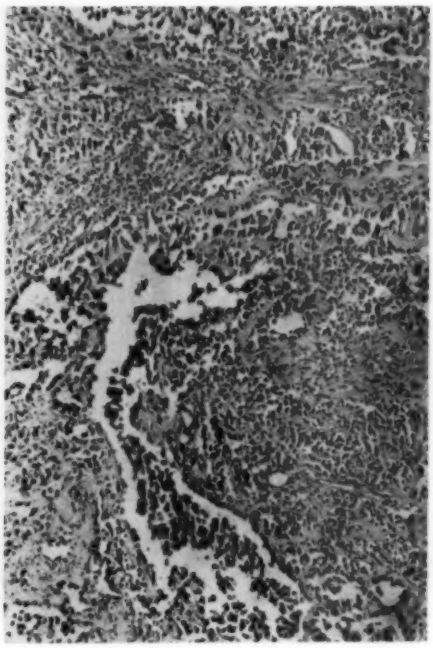


Figure 1D

Fig. 1D (Case 1).—Biopsy of thoracic tumor. Tumor is partly differentiated. Trabeculae, both coarse and fine, separate groups of tumor cells which appear to line the trabeculae but are free in the larger lumens. Some of the free cells and a few lining cells show eosinophilic granules and resemble granular myoblasts. Reduced about 40% from mag. × 75.

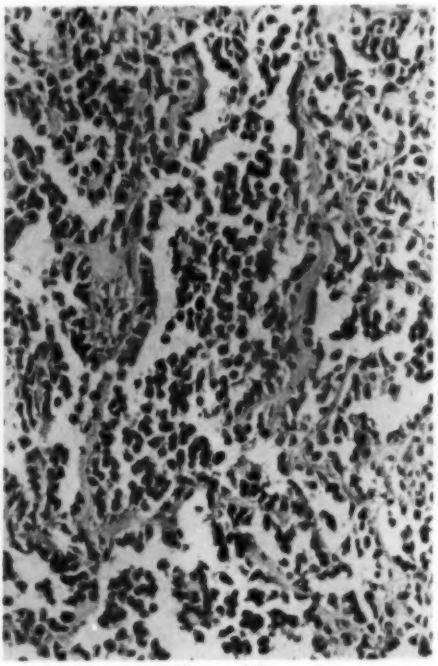


Figure 1E

Fig. 1E (Case 1).—The cells lining the trabeculae are small and undifferentiated. A few of the cells in the lumens show granules and resemble granular myoblasts. Reduced about 40% from mag. × 200.

bands of fibrous tissue, which separated small clusters or columns of pleomorphic cells. In the center of the tumor there were several large tumor-filled multilocular spaces which were otherwise similar. In this area the pattern closely resembles the findings in Cases 3 and 4. Throughout the section, rows of small cells covered the surfaces of the trabeculae. Some elongated tumor cells invaded the trabeculae, lying between fibers. Most of the tumor cells were small and roughly rounded; many contained sparse red granules with the trichrome stain.

A Foot stain showed a network of coarse fibers, corresponding to the trabecular pattern and separating groups of cells. The broad trabeculae in the area of larger spaces showed coarse reticulum fibers along each surface and a fine network between.

Diagnosis: Embryonal rhabdomyosarcoma.

Course: The patient died at 32 months of age, 9 days after admission. Fever developed on the sixth day of hospital residence; breathing became more labored, and cardiac contractions, irregular. Cortisone was given daily, without apparent benefit. The patient survived for six months after first detection of thoracic swelling.

Case 2.—A white boy 6½ years of age had been well until 30 days before admission, when he fell from his bicycle onto the lawn and injured his right shoulder. His father saw the fall and considered the accident and injury trivial. Pain persisted in the right shoulder, and 24 hours after the fall radiographic examination disclosed patchy destruction in the proximal metaphysis of the humerus, with an incomplete fracture through the same levels. Six days after the injury pain with marked limitation of motion developed in the other shoulder, the left, and then within a few hours this became so severe that the boy could not lift food to his mouth with either hand. Eleven days after the shoulder injury a large flat painless swelling was first noticed just above the right ankle.

Owing to the pain and disability at the shoulders, the shoulders were reexamined radiographically 15 days after the injury; deep zones of destruction

were now evident at the proximal ends of the humeral shafts, with transverse pathological fractures. About 20 days after the first shoulder injury the patient's back became painful and stiff at the midthoracic level, and, at this time, films of the entire skeleton disclosed that the sixth dorsal vertebra was partially destroyed and collapsed and that a large segment of the right ilium was demineralized. The boy had stopped walking and sitting, and he moved little, owing to intense bone pain which was exaggerated by both active and passive movements. He lost two and one-half lb. during the first month. Three treatments (total of 500 r) of external irradiation were given at the local hospital before admission here.

His father and mother were living and well, 42 and 44 years of age, respectively. A brother, 8 years of age, had always been healthy. There were no known deaths from neoplastic disease in the family.

Physical Findings.—Nutrition was good, but the patient was uncomfortable and apprehensive, and even slight movements of the head, shoulders, spine, and right hip were slow and guarded.

Fig. 2A (Case 2).—Findings in the left humerus. Early destructive changes in proximal end, with pathological fracture.

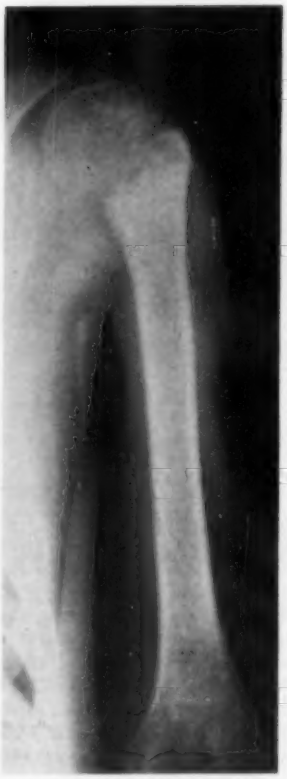


Fig. 2B (Case 2).—Findings in the left humerus. Six weeks later and after 1300 r of external treatment, much of the lesion has remineralized.

Movements at the shoulders were limited in all directions. Grip in both hands was surprisingly strong. On the lateral aspect of the right shank just above the ankle there was a flat swelling about 20 cm. in length; it was painless and nontender, and the skin over it, although tight and shiny, was intact. There were no other swellings, palpable or visible, in the soft tissues. He would not move voluntarily and resisted passive motion, crying out with pain when this was attempted. Tenderness, muscular spasm, and limitation of motion were most marked at both shoulders, middorsal spine, and right hip.

Radiological Findings.—Destructive lesions were identified in the proximal third of each humerus, the sixth thoracic vertebra, the right ilium, and the right scapula (Figs. 2A to 2F). It should be emphasized that the right tibia and fibula, under the swelling on the right shank, were normal radiographically in both early and late examinations.

Fig. 2C (Case 2).—Destruction and collapse of sixth dorsal vertebral body on Oct. 4, 1956. Its left pedicle is destroyed.

Fig. 2D (Case 2).—Sclerosis of the collapsed sixth vertebral body six weeks later and after 1900 r of external irradiation.

Laboratory Findings.—Hemoglobin was 10.3 gm. per 100 cc.; RBC, 3,800,000 per cubic millimeter; WBC, 5500 per cubic millimeter, with 61% polymorphonuclear cells, 24% lymphocytes, 9% monocytes, 5% eosinophils, and 1% basophils. Two weeks later monocytes had diminished to 2%, and eosinophils, to 2%. Schilling count was normal, as were the clotting and bleeding times. The sternal marrow was hypercellular, chiefly in the monocytic and eosinophilic series; neoplastic cells were not seen. The rate of sedimentation of the erythrocytes was 37 mm. after one hour on admission; it was 26 mm. one week later.

Serum contained 12.9 mg. of calcium per 100 cc. and 6.4 gm. of phosphorus. Serum alkaline phosphatase activity equaled 41 Bodansky units.

Urine was normal clinically and cytologically; there was no Bence Jones protein in the urine.

Biopsy of Leg Tumor.—Of several small fragments of tumor the largest is 2×5 mm. Small sheets or clumps of pleomorphic cells are separated by fairly wide bands of young connective tissue.

Fig. 2E (Case 2).—Segmental demineralization and destruction of the lower part of the right ilium, with compression fracture of the roof of the acetabulum.

Fig. 2F (Case 2).—Six weeks after Figure 2E much of the right ilium has remineralized but the compression deformity of the ilium is more evident. External irradiation, 1600 r, had been applied to the right ilium since Figure 2E. Notwithstanding, large new destructive neoplastic foci have appeared in the right pubic and ischial bones and in the left ilium and ischium.

At the margins the tumor invades between fat cells and forms spidery thin bands between tendon fibers. The picture closely resembles that in Case 5. With a trichrome stain many cells contain moderate numbers of fuchsinophilic granules.

Diagnosis: Embryonal rhabdomyosarcoma.

Course.—External irradiation was given to both shoulders, to the midthoracic spine and later to the right side of the pelvis, and then later to the primary mass in the right shank. Cortisone by mouth was begun early in large doses. Total roentgen dose to the skeleton was 13,000 r. The immediate response to this treatment was excellent. Within five days practically all of the pain disappeared and his movements and later activity became practically normal, except walking. He sat up without pain or fear of pain but refused to walk, owing to pain and fear of pain in the left leg. He returned home. Repeated radiographic examination disclosed that new destructive changes were developing and extending in the skeleton, while the destructive changes in the sites of irradiation were healing. The remission lasted for about five weeks, after which pain and muscular spasms became severer and more generalized. After a few weeks the patient became completely immobilized again, despite continuation of irradiation and steroids. Massive doses of opiates gave him considerable relief in the terminal stages. He died at home 3 months and 21 days after the first sign of the disease—pain in the shoulder which followed a fall from his bicycle.

Case 3.—An Italian boy 9 years of age was referred to us by another hospital. Six weeks previously a small swelling appeared in the dorsum of his right foot and then slowly enlarged. It had not been painful or discolored, and he had had no constitutional signs. A piece of the swelling was excised, and the microscopic changes had suggested a malignant synovioma. Birth, family, and personal histories were all noncontributory. The healthy father and mother were 42 and 34 years of age, respectively. Two older brothers, 15 and 13 years of age, were healthy. Neoplastic disease had not been recognized in the family.

Physical Findings.—Nutrition was good; growth and development were normal. The single abnormal findings was a large hard fixed swelling in the right foot which projected dorsad but was not tender or discolored. The overlying skin was intact. Regional lymphatic vessels and nodes were normal clinically.

Laboratory Findings.—Blood and urine were normal. Hemoglobin equaled 14.8 gm. per 100 cc.; RBC, 4,900,000 per cubic millimeter; WBC, 13,000 per cubic millimeter, with 50% polymorphonuclear cells, 42% lymphocytes, 6% monocytes, and 2% eosinophils.

Radiological Findings.—The entire skeleton was examined, and the only abnormalities were in the right foot, where a large spindle-shaped tumor of water density spread the first and second metatarsals (Figs. 3A to 3E). There was no clinical evidence at this time, six weeks after first appearance of the swelling, of hematogenous metastases.

Course.—A small piece of the tumor was excised for microscopic examination and tissue culture.

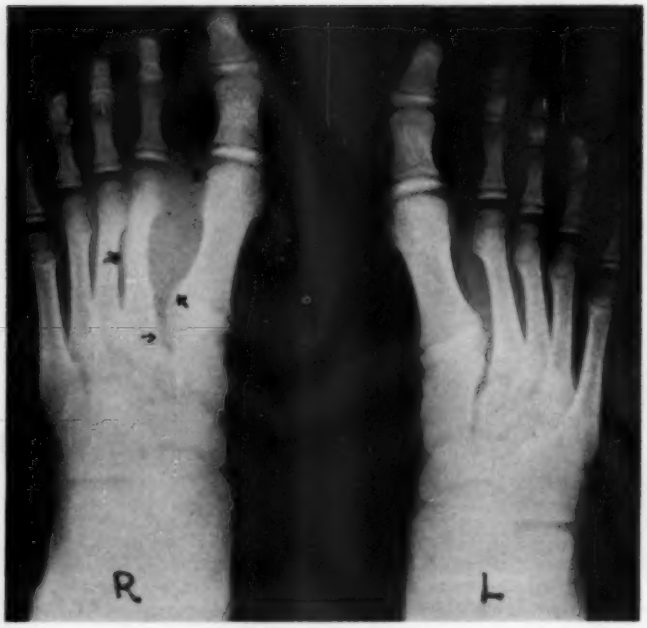


Fig. 3A (Case 3).—Films of the feet. The primary tumor spreads the first and second right metatarsals. The latter is bowed, and its medial edge, contiguous to the tumor, is irregular. There is no destruction in either bone to suggest direct extension from the primary tumor. This film was made six weeks after the mother first noticed a swelling on the dorsum of the right foot.

The findings by both techniques indicated tissue of high malignancy, probably a rhabdomyosarcoma. The foot was amputated at the ankle by the Syme procedure, 72 days after the tumor was first noticed by the mother. The patient then went home and appeared to do well and remained asymptomatic for approximately seven months after onset, when pain developed in the left leg. Deep pain then appeared in both legs (shortly after the amputation) and soon became so severe that it was relieved only by heavy sedation. Motion of the legs, however, was not impaired. Eight months after onset, radiographic findings in the skeleton were still normal save for the disuse rarefaction and atrophy which had developed in the right femur following amputation of the right foot. The right regional lymph nodes became swollen, and specimens of them suggested malignant rhabdomyoma in both microscopic sections and tissue cultures. The patient became much more comfortable with external x-irradiation and was discharged home to spend Christmas. His condition worsened after

Fig. 3B (Case 3).—Eight months after the appearance of pedal swelling, the skull is normal radiographically.

Fig. 3C (Case 3).—Seven and one-half weeks after Figure 3B, large segments of the frontal squamosa and of the parietal bones contain multiple large and small destructive foci. Similar sudden appearance of bone lesions late in the disease is characteristic of other patients.

a few weeks, and he was reported to have died without further treatment 11 months after the first appearance of the swelling in the right foot.

Widely scattered destructive neoplastic foci were found in the skeleton in films made nine months after onset—in long bones, pelvic bones, and skull (Figs. 3A to 3E)—but the spine was normal. At the same time, the hilar images at the roots of the lungs were enlarged, which raised the question of neoplastic metastases in these structures.

Findings in Specimen from Foot (Figs. 3F and 3G).—The tumor has an alveolar or honey-comb structure. There are broad fibrous trabeculae containing vessels or lacunae in which are masses of pleomorphic cells. The trabeculae are lined by a single row of small crowded round cells with somewhat irregular nuclei and scanty cytoplasm. The cells appear set into depressions in the surfaces of the trabeculae, and no basement membrane separates them. The cells in the lumens of the

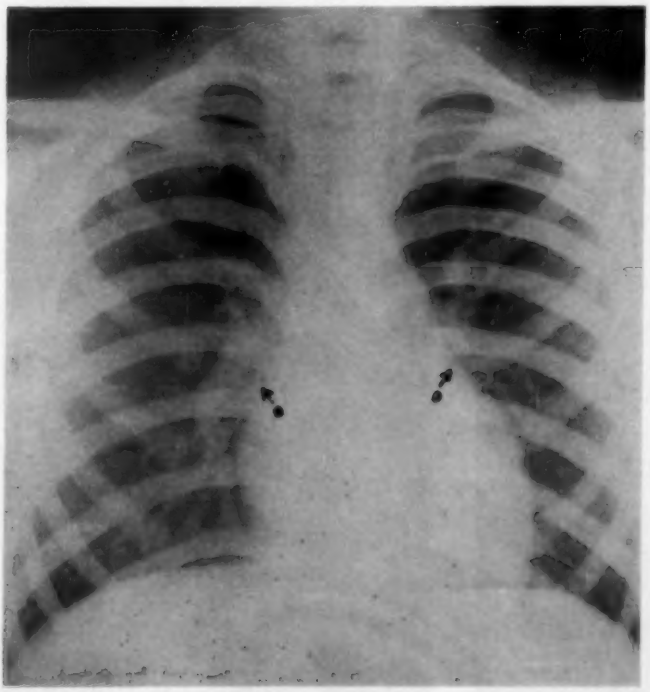


Fig. 3D (Case 3).—The chest is normal six weeks after onset of pedal swelling.

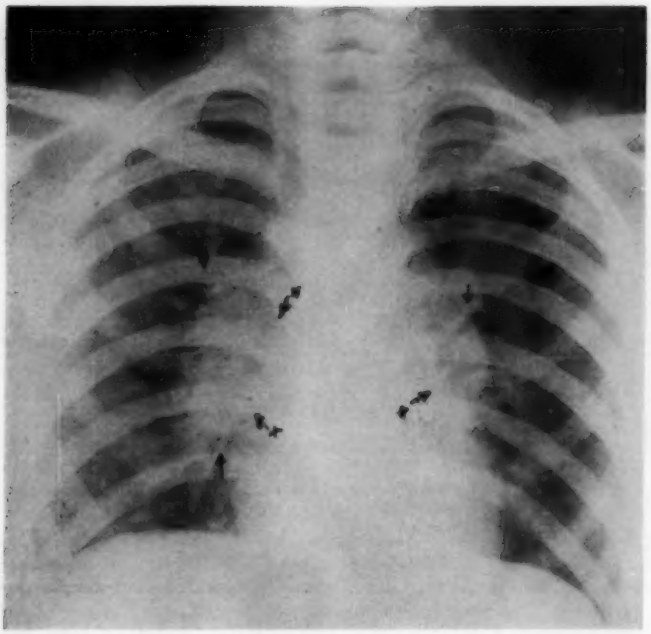


Fig. 3E (Case 3).—Nine and one-half months after onset the hilar nodes are greatly enlarged. The nature of these swellings was not proved; there was no necropsy. Patient died two and one-half months after Figure 3E was made.

Fig. 3F (Case 3).—Biopsy specimen from inguinal lymph node. Tumor contains coarse trabeculation with pleomorphic cells in the lacunas. The cells lining the trabeculae are small and less differentiated than those in the lumens. The latter include granular myoblasts. Occasional elongate cells with few cross striations were present along the margins of the tumor. Reduced about 43% from mag. × 130.

Figure 3F

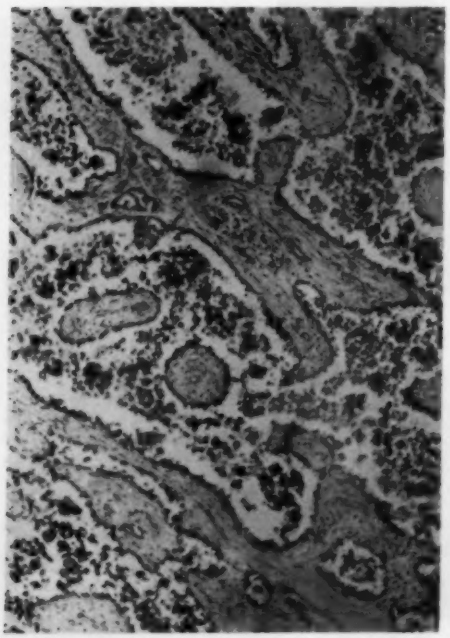
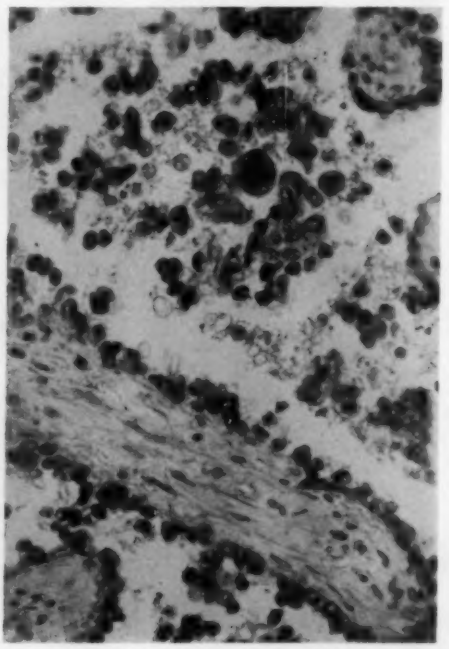


Fig. 3G (Case 3).—This higher magnification shows the pleomorphism and intimate relation of trabeculae and lining cells. Reduced about 43% from mag. × 400.

Figure 3G



trabeculae vary in size, and a few are large and multinucleated; some large cells are degenerated. With a trichrome stain most of the cells, both large and small, contain fuchsinophil granules and resemble granular myoblasts. In some areas the trabeculae are thin and the lacunae are small; few large multinucleated cells are found in these areas, though pyknotic and degenerating cells are present. In a few areas at the margin of the tumor there are compact masses of pleomorphic cells without distinct trabeculation. The tumor invades adjacent fat and connective tissue. A few ribbon cells are seen here, and occasional ones show a few longitudinal striations. No cross striations are seen. In invading fibrous tissue the cells also form clumps or columns with crowded pleomorphic nuclei. One gains the impression that the areas with heavy trabeculation are older portions of tumor, while the nests and sheets at the margin are younger and actively invading cells.

Findings in Lymph Node.—The structure is similar. Coarse and fine trabeculae are formed. The peripheral sinus contains masses of cells and is lined in a manner similar to the tumor trabeculae. Tumor cells are found in adjacent lymphatics.

Diagnosis: Embryonal rhabdomyosarcoma.

CASE 4.—A Jewish boy 52 months of age bumped his face against a doorknob and cut the right upper eyelid. Four weeks later the eye began to protrude from the orbit and the orbital tissues became swollen. Two weeks after onset of exophthalmus he was first examined here. The father, 34 years of age; the mother, 33 years of age, and a sister, 2 months of age, were all living and well. The patient was born normally after normal gestation. He was healthy until the 24th month, when swellings appeared in the right submandibular region; these drained externally later. They were removed surgically, and the parents were told that the nodes were tuberculous. Tonsils and adenoids were removed a few weeks later, and these also were found to be tuberculous.

At his first examination, two weeks after the onset of exophthalmus, there were no neurological deficits and the swelling of the right orbit was not painful. Abnormal physical signs included tight right-sided irreducible exophthalmus, paralysis of the right external rectus muscle, limitation of right ocular movements in all directions, and papilledema of 3 D. In the swelling of the right orbit a separate mass was palpated in the inferior lateral quadrant. The voice had a nasal quality. The tuberculin skin test was positive.

Laboratory Findings.—Hemoglobin, 14.2 gm. per 100 cc.; RBC, 4,900,000 per cubic millimeter; WBC, 8600 per cubic millimeter, with 57% polymorphonuclear cells, 42% lymphocytes, and 1% monocytes. ESR equaled 16 mm. after one hour. Serum phosphatase activity in the serum equaled 44 Bodansky units.

Radiographic Findings.—Radiographic findings indicated an excessive amount of soft tissue in the right orbit, without evidence of extension into contiguous bone. A calcifying primary tuberculous complex was found in the left lung and left side of the mediastinum. The right orbit was explored by Kroenlein's technique, and a large tumor was found which surrounded the optic nerve. In microscopic sections of this tumor, a highly cellular and malignant tissue was found. The malignant cells were so primitive and undifferentiated that they could not be classified satisfactorily by several expert pathologists.

Treatment and Course.—X-irradiation was applied to the right orbital region and was continued for several weeks, until 10,000 r had been given.

A recurrent neoplasm was palpated in the right orbit 3½ months after onset of exophthalmus, when the patient was 56½ months of age. At this time the patient complained of pain in the back; a few weeks later destruction and compression of lower dorsal vertebrae were identified radiographically. His back became stiff, and he had great difficulty in rising from recumbent to erect position. Sedimentation of the erythrocytes now equaled 36 mm. after one hour, and two weeks later this increased to 110 mm. after one hour. The right sacroiliac region next became tender. Nutrition was still surprisingly good; hemoglobin was 11 gm. per 100 cc., and RBC numbered 4,700,000 per cubic millimeter. During the following weeks both red and white blood cells diminished rapidly, owing in part to the heavy irradiation of the skeleton. The patient's general condition worsened gradually, and bone pain increased. He became weak, febrile, and apprehensive. He died in the hospital approximately 10 months after the exophthalmus was first noticed.

In radiographs of the entire skeleton the findings were normal during the early months of the illness, but, later, widely scattered destructive neoplastic foci appeared in long bones, spine, pelvis, and shoulder girdle (Figs. 4A to 4F). Late films of the cranium were not made. The lungs were free of metastasis in films made late in the disease.

Necropsy.—At necropsy, neoplastic foci were found in the calvarium (frontal and parietal bones), spine, long bones, and one paravertebral lymph node. Several vertebral bodies exhibited fractures. Metastatic calcifications in the kidneys were thought to be secondary to the extensive bone destruction. In both kidneys, changes suggested glomerulonephritis. There were no neoplastic foci in the spleen, liver, kidneys, or lungs. Microscopic changes indicated a highly cellular malignant tissue.

Fig. 4A (Case 4).—Six months after onset, there is a single large destructive focus in each femoral metaphysis, medially placed in the right femur and laterally placed in the left. Tibias are normal.

Fig. 4B (Case 4).—Thirty-seven days after Figure 4A, there are deep bands of destruction in the metaphyses of both femurs and both tibias. Femoral and tibial ossification centers are normal.

Biopsy Specimen of Paravertebral Tumor (Figs. 4G and 4H).—The tumor has a framework of coarse fibrous trabeculae carrying vessels. Within the spaces there are masses of widely varying pleomorphic cells. With a trichrome stain the majority of both small cells and larger multinuclear cells contain red cytoplasmic granules. Small tumor cells form rows against the trabeculae but also invade them. A few elongated tumor cells lie between fibers in the septa, and some tadpole and ribbon cells lie in the lacunae. Longitudinal but no cross striations are found in them. This

Fig. 4C (Case 4).—Six months after onset, the pelvis is normal radiographically.

Fig. 4D (Case 4).—X-ray film made 37 days after Figure 4C, all of the pelvic bones and both femurs show extensive destruction.

Fig. 4E (Case 4).—Six months after onset, the spine is normal.

Figure 4E

Fig. 4F (Case 4).—X-ray film made 37 days after Figure 4E; destruction and compression deformities are evident at several levels in the spine (arrows at thoracic 2, 4, 8, 9 and lumbar 1).

Figure 4F

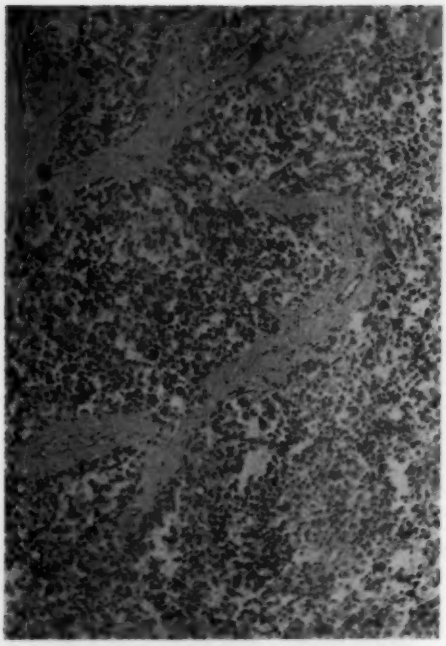


Figure 4G

Fig. 4G (Case 4).—Microscopic findings in the most differentiated tumor in the group. Many large granular myoblasts are included among the pleomorphic cells between the trabeculae, and there are a few elongated cells with cross striations. Reduced about 40% from mag. × 130.

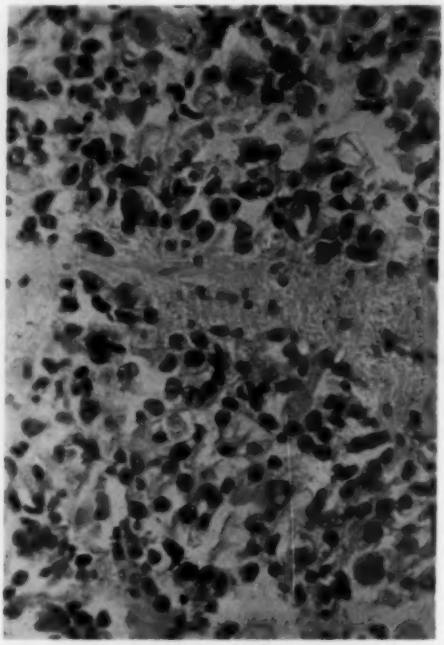


Figure 4H

Fig. 4H (Case 4).—Cells lining the trabeculae appear to rest in depressions. There is no basement membrane. Cells in the humerus show pleomorphism. Reduced about 40% from mag. × 400.

tumor and that in Case 3 are the most fully developed as to trabeculae and abundance of granules in the cells.

Diagnosis: Embryonal rhabdomyosarcoma.

CASE 5.—An 11½-year-old white boy was admitted with the complaint of severe back pain of about eight hours' duration. For four months the patient had complained of slight pain at the mid and low back region on several occasions. These complaints were attributed to minor trauma and accidental falls. The patient had had brief episodes of slight discomfort at the midportion of the left foot on several occasions during the previous two to three months. Pain located at the upper dorsal and lower lumbar spine had been produced by flexion of the neck during the preceding 10 days.

Examination revealed a well-developed and well-nourished boy. His neck was stiff, and there was resistance to flexion of the neck associated with increased pain in the lumbosacral area. The patient could not flex the trunk or sit because of the increased pain. There was a full range of motion in the joints of the extremities, and muscular strength appeared to be normal. The spinous processes were not tender. Babinski's reflex at the left foot was the only abnormal neurological sign.

An ESR of 56 mm. in an hour and a moderate polymorphonuclear leukocytosis were present on admission. The hemoglobin concentration, urinalysis, serum calcium, serum phosphorus, serum alkaline phosphatase activity, and serum albumin and globulin concentrations were all normal.

Radiographs were made of the skeleton, including the skull, shoulder girdle and thorax, pelvis, and long bones (Figs. 5A to 5E). Abnormalities were limited to the spine. Destruction and partial collapse of the body of the third dorsal vertebra were associated with the shadow of a paraspinal mass. The body of the 12th dorsal vertebra was flattened cephalocaudally to about one-half its normal altitude, with some wedging ventrad. In addition to the compression, the body was rarefied and the interpediculate space was greater in this vertebra than in the contiguous ones. All of the lumbar vertebral bodies were slightly rarefied, and

Figure 5A

Fig. 5A (Case 5).—A few weeks after onset of vague pain in the back, the spine is normal radiographically.

Figure 5B

Fig. 5B (Case 5).—Eight weeks after Figure 5A, and at the time of first appearance of severe pain in the back, the first, third, and fifth lumbar bodies are compressed and the contiguous intervertebral spaces are widened. X-ray slightly retouched.

Fig. 5C (Case 5).—Knees, six months after onset of back pain, show extensive metaphyseal rarefaction.

Fig. 5D (Case 5).—Left foot three months after onset of vague back pain; a small tumor of water density spreads the first and second metatarsals. These bones are normal.

Fig. 5E (Case 5).—X-ray made two months after Figure 5D; the enlarged tumor spreads the bones more widely, with suggestion of marginal destruction of second metatarsal.

the second and fourth lumbar vertebral bodies were slightly flattened cephalocaudally.

Findings in an intravenous pyelogram were normal. Marrow smears obtained by aspiration of the iliac crests were normal microscopically.

During the first four days in the hospital the patient often complained of severe headache, nausea, vomiting, and pains in the lower extremities, for which meperidine (Demerol) was required. During this period, diffuse weakness of both legs and sensory and motor signs of spinal cord compression appeared. Six days after admission a laminectomy including segments T-11 through L-1 was performed. No intradural tumor was found. At this exploration a trocar biopsy of the body of the partially collapsed 12th dorsal vertebra was done. Sections of this biopsy specimen showed cancellous bone with marginal resorption and necrosis. Portions of the blood-forming marrow were replaced by immature fibrous connective tissue, between strands of which there were several large and pleomorphic mononuclear cells. No mitoses were seen. These abnormal cells resembled either histiocytes or neoplastic cells. The evaluation of this biopsy specimen was difficult because of the effects of the pathological fracture and necrosis. After the laminectomy, the weakness of both lower extremities and the neurological signs of cord compression became severer and the patient was unable to void. Hypesthesia extended to the sixth dorsal dermatome. On the 12th hospital day a laminectomy from T-1 to T-3 was performed. A large epidural tumor was found at the ventral aspect of the neural canal, extending laterally to the paraspinal soft tissues. Spinal cord compression was relieved by the removal of a large portion of this tumor. The microscopic appearance of this specimen was that of a highly cellular small-cell tumor which was diffusely invading dense fibrous tissue and fat.

After the thoracic laminectomy the patient improved; voluntary motion returned in the legs, and there was improvement in the neurological signs previously present. Radiotherapy was begun 3 weeks after admission, with irradiation of the entire spine, and was completed 17 days later. The patient received a total dose of 2450 r in air to the spine. This was calculated to have delivered 2500 r tumor dose to the spine. During and subsequent to this treatment there was a marked subsidence of the back pain and a slower but continuous decrease of the neurological abnormalities in the legs.

Repeat radiographic examination of the skeleton during the period of radiotherapy revealed shallow metaphyseal rarefaction under the provisional zone on calcification in the long bones of the extremities. A slight diffuse rarefaction of the bony pelvis was present. These abnormalities were highly suggestive of early neoplastic disease, but it was difficult to separate neoplastic destruction from atrophy and demineralization of disuse. When the patient was examined three months after admission he appeared emaciated and chronically ill but offered few complaints other than pain at the left shoulder. Painless tumors of the soft tissues overlying the calvarium and at the dorsum of the left foot were present. Anemia (hemoglobin, 7.8 gm.) was present, but the WBC, peripheral blood smear, and platelet concentration were normal. Radiographic examination of the skeleton and chest was repeated at this time.

The patient died at home four months after the onset of severe acute pain in the spine and about eight months after the beginning of vague transitory pains in the spine. At the time of death, the primary tumor in the left foot had swollen

Figure 5F

Fig. 5F (Case 5).—Microscopic view of vertebra. Marrow cavity contains undifferentiated tumor cells. These have infiltrated the periosteum. Diagnosis: Undifferentiated malignant tumor. Reduced about 40% from mag. × 40.

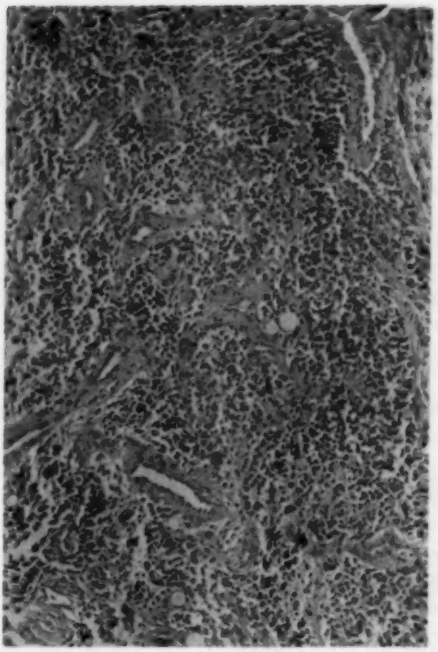


Figure 5G

Fig. 5G (Case 5).—Microscopic view of epidural mass shows partial differentiation with coarse trabeculae separating groups of pleomorphic cells, many of which contain granules and resemble granular myoblasts. Diagnosis: Embryonal rhabdomyosarcoma. Reduced about 40% from mag. × 75.

progressively until it became more than twice as large as the normal right foot.

Findings in Two Biopsies (Figs. 5F and 5G).—Bone Biopsy, Vertebral Body: The marrow spaces beneath the cortex are filled with tumor cells having pleomorphic nuclei with bosselated surfaces. The cytoplasm is often poorly defined but is sometimes granular and eosinophilic. The periosteum and adherent tendons are invaded by tumor which here appears as crowded nests of cells or bands of elongated cells with hyperchromatic nuclei. The diagnosis on the basis of this section is undifferentiated tumor, type not identified.

Tumor from Meninges: The tumor forms nests and columns of cells in a matrix of loose young connective tissue. The nuclei are billowy and pleomorphic. The cytoplasm is often vacuolated and occasionally contains a few fuchsinophil granules. A very few ribbon cells but no cross striations are seen.

Diagnosis: Embryonal rhabdomyosarcoma.

Comment

Of these five patients, four were white boys. A Negro girl, 2½ years of age, was the youngest in the group. The oldest boy was 11½ years of age. The first sign of disease in three patients was the appearance of the primary swellings—located in the dorsal thoracic wall in one, in the foot in another, and in the orbit in the third. In the two remaining patients, pain and limitation of motion at the sites of secondary tumors in the skeleton—in a shoulder in one case and in the lumbar spine in the second—were the initial clinical manifestations. In both of these patients, in retrospect, primary tumors were present early—one near an ankle and the second in the foot—but they had been overlooked in the earlier examinations. In Case 5 the tumor

in the foot was visible early when the first films were made (Fig. 5D). The swelling at the ankle in Case 2 was clearly visible and palpable at our first examination, although it had not been noted previously. The early clinical silence of these primary tumors, the absence of pain and tenderness, reduces the probability of their early clinical recognition. In all cases there is no radiographic evidence of direct extension from the primary tumors to contiguous bones, notwithstanding widely scattered dissemination to the skeleton, presumably by way of the blood stream. In all cases, early, there were no constitutional signs of disease.

Primary neuroblastomas do not occur in the sites occupied by these primary rhabdomyosarcomas,[6-10] and this feature makes possible the clinical differentiation of rhabdomyosarcoma and neuroblastoma. A single case of primary neuroblastoma in the skin of the thigh has been reported,[11] in which following excision recovery was complete without metastasis to the skeleton. The sarcoma of the foot of an infant reported by Fahey and Bollinger[12] has microscopic features consistent with rhabdomyosarcoma; skeletal metastases were not recognized.

Radiographic skeletal changes of these metastatic rhabdomyosarcomas were almost exclusively destructive, and they resembled the skeletal findings of neuroblastoma, both in the character of single lesions and in their pattern of distribution in different bones. According to our experience, the spine was affected more frequently and more extensively in these rhabdomyosarcomas than in neuroblastoma, but it is clear that these two diseases cannot be satisfactorily differentiated except by microscopic findings. The radiographic findings in the spine are also similar in rhabdomyosarcoma and eosinophilic granuloma; the latter was the first radiographic diagnosis in Cases 2 and 5.

Laboratory findings are important from both the positive and the negative aspects of diagnosis. Characteristic changes in the blood and bone marrow smears should readily differentiate multiple leukemic bone lesions from those of metastatic skeletal rhabdomyosarcomas. It is surprising that rhabdomyoblasts were not found in the bone marrow smears in Cases 2 and 5, in view of the widely scattered destructive neoplastic foci in many bones. Phosphatase activity in the serum was increased to 41 and 44 Bodansky units in two cases, and the ESR was accelerated in three cases.

Biopsy specimens of the primary and metastatic lesions and of tissue cultures in microscopic sections provide the only means of satisfactory conclusive diagnosis. Even microscopic changes may be uncertain, owing to the primitive character of the poorly differentiated myoblasts and their variations.

Variations in the pattern of this tumor occur within different areas of the same mass and at different times in the same case. Interval evidence suggests that these alterations may be produced by response of the tumor cells to their cellular environment, by maturation, and by irradiation. Thus the central and presumably older portions may show very coarse trabeculation, many large multinucleated granular myelocytes, and a greater number of elongated forms, while along the newly growing margin of the tumor the cells are smaller, without trabeculae, and with fewer granules. On invading tendon or dense collagen, the cells form strands of elongate, tadpole, or ribbon cells, with occasional small clusters of rounded cells when a space is reached. Under mucous or serous surfaces the tumor forms polypoid tongues (sarcoma botryoides). In our series, this has been observed in the pericardium and in the vagina.

Since wide variations may occur in the same section of tumor, and since in the more cellular immature areas the cells are so undifferentiated as to be difficult, if not impossible, to identify, multiple sections or

a second biopsy may be required to establish the diagnosis.

The use of the term embryonal rhabdomyosarcoma for these tumors is based on the desire to distinguish them from the anaplastic myosarcomas of the adult and also from malignant granular-cell myoblastomas. These tumors, embryonal rhabdomyosarcomas, occur chiefly in children, are pleomorphic, contain undifferentiated cells, and metastasize chiefly to the regional nodes, to bone, and, sometimes, to lung. There is often differentiation of the tumor between the time of the initial biopsy and the time of a later biopsy or postmortem examination, a few months later. Response to radiotherapy may be gratifying at first, but the tumor recurs, and no prolonged cures have been reported.

The identifying histolgical features are the pleomorphism; the pattern of nests of cells in the lacunae of a network of collagen fibers; the irregular bosselated appearance of the nuclei in less-well-differentiated cells; the presence of fuchsinophil granules in many of the cells, both large and small; the row of small cells along the trabeculae, each set in a depression, and lack of a basement membrane. Strap or ribbon cells may be absent, but a few are usually present along the growing margins, especially in the maturer tumors.

Although many of these tumors arise in skeletal muscle, there are recorded instances of origin from many tissues of the body. The commonest nonmuscle sites of origin are dermis, alimentary tract, and pelvic organs. It is possible to conceive of the cell of origin as a pluripotential near-ancestor of the myoblast, both because of the varied sites of origin and because of the pleomorphism of the tumor itself. It appears to belong to the group of embryonal tumors, which also includes adrenal neuroblastomas, which are the basis for Cohnheim's theory of origin of tumors as congenital embryonal rests.

External irradiation was very effective initially in the four cases in which it could be used satisfactorily; in Case 1 there was no response to irradiation, but death occurred within a few days after irradiation was begun. Pain, tenderness, muscular spasm, and limitation of motion all were greatly improved after a few days of radiation therapy, and it provided several weeks of pain-free life for those patients who were suffering excruciating bone pain. However, in all cases, after treatment had continued for six to eight weeks, relapses set in and irradiation became wholly ineffective; new skeletal tumors appeared and grew rapidly in the sites of irradiation. Cortisone also brought much relief in Case 2 for an initial period of several weeks.

Recognition and accurate classification of embryonal rhabdomyosarcoma are of more than academic interest; they are essential for better knowledge of the course and pathogenesis of this neoplasm and possibly important from the standpoint of developing specific chemotherapeutic agents against it. Also, it seems to us that it is important to recognize rhabdomyosarcoma so that it will not be confused with neuroblastoma and included erroneously in the studies of chemotherapeutic results with neuroblastoma.

Summary

Clinical, radiographic, and microscopic features of metastatic embryonal rhabdomyosarcoma in the growing skeleton are described in five children. These are the first recorded radiographic descriptions of scattered multiple metastases to the growing skeleton by this neoplasm. The presence of primary rhabdomyosarcomas in sites never occupied by the primary neuroblastomas appears to be a sound clinical feature for differentiating these two tumors, although their skeletal metastases are similar radiographically. When multiple scattered destructive lesions of the growing skeleton are observed radiographically, embryonal rhabdomyosarcoma should be included in the differential diagnosis along

with neuroblastoma, leukemia, and retinoblastoma.

Babies Hospital, Broadway and 167th St. (32).

REFERENCES

1. Stout, A. P.: Rhabdomyosarcoma of Skeletal Muscle, Ann. Surg. 123:447, 1946.

2. Stout, A. P.: Tumors of the Soft Tissues, Atlas of Tumor Pathology, Sec. 2, Fasc. 5, Armed Forces Institute of Pathology, Washington, D. C., 1953.

3. Stobbe, G. D., and Dargeon, H. W.: Embryonal Rhabdomyosarcoma of Head and Neck in Children, Cancer 3:826, 1950.

4. Horn, R. C., Jr., and Enterline, H. T.: Rhabdomyosarcoma: A Clinicopathologic Study and Classification of 39 Cases, Cancer 11:181, 1958.

5. Pack, A. T., and Eberhart, W. F.: Rhabdomyosarcoma of Skeletal Muscle, Surgery 32: 1023, 1952.

6. Andersen, D. H.: Tumors of Infancy and Childhood, Cancer 4:890, 1951.

7. Hansman, C. F., and Girdany, B. R.: Roentgenographic Findings Associated with Neuroblastoma, J. Pediat. 51:621, 1957.

8. Kincaid, O. W., and others: Neuroblastoma: A Roentgenologic and Pathologic Study, Am. J. Roentgenol. 78:420, 1957.

9. Sherman, R. S., and Leaming, R.: The Roentgen Findings in Neuroblastoma, Radiology 60:837, 1953.

10. Wittenborg, M. H.: Roentgen Therapy of Neuroblastoma: A Review of 73 Cases, Radiology 54:629, 1950.

11. Jacobsen, V. C., and Hosoi, K.: Primary Sympathicoblastoma of the Skin of the Thigh, Am. J. Path. 6:427, 1930.

12. Fahey, J. J., and Bollinger, J. A.: Congenital Sarcoma of the Foot: Case Report and Review of Literature, A. M. A. Am. J. Dis. Child. 86: 23, 1953.

Relationship of Measles and Distemper

JOHN M. ADAMS, M.D.; DAVID T. IMAGAWA, Ph.D.; DAVID L. CHADWICK, M.D.; EMILY H. GATES, M.D., and ROBERT A. SIEM, Ph.D., Los Angeles

Although measles (rubeola) and canine distemper must still be considered as distinct clinical entities, there appear to be certain clear-cut relationships between these diseases. Both are characterized by a high degree of contagiousness and have almost identical incubation periods in their respective natural hosts, man and dog. The striking symptoms in both diseases are largely respiratory and consist of fever, cough, coryza, and conjunctivitis. Characteristic rashes are evident, and in the animal they are seen around the mouth and on the chin and abdomen. Demyelinating encephalitis occurs in both measles and distemper in a small proportion of the cases. The most striking similarities may be seen in the pathologic and immunologic findings, which will be the main points to be emphasized in this paper.

Both diseases are caused by viruses, the basic characteristics of which are not fully understood and may prove to be different in many fundamental respects, such as their failure to multiply and cause cytopathology in certain tissue cultures. The measles virus has been shown to multiply readily in most human cell cultures, such as the HeLa,[1] Hep-2,[2] KB,[3] and FL * cells, as well as other human and monkey tissue cultures.[5] Recently the measles virus has also been adapted to suckling mice in our laboratory, which makes it possible for the first time to study these viruses in the same species. The canine distemper strains of virus cause disease primarily in the canidae family (dog) and the mustelidae family, comprising the mink, ferret, and martin. The virus has been successfully adapted to the chick embryo [6] and to mice.[7-9] It should be pointed out, however, that the canine distemper virus has not been successfully adapted to the same cell lines which support the growth of measles virus. A recent report from the Institute of Virology, Moscow, by Riazantzeva,[10] indicates that experimental measles has been successfully produced in puppies of the canine family. The report states that 48 puppies were inoculated with washings and blood from patients with measles and that fever was produced in 50% of the animals, with catarrh and rash in 38%. Viremia occurred in 100% of the puppies two to eight days following inoculation. The passage experiments were positive, with viremia occurring in 100%, fever in 65%, and rash in 40% of the animals. Antibodies developed which neutralized measles virus from monkey and man.

In this paper we shall present data of a pathological nature from human cases of measles and compare these findings with experimental distemper in animals. The cytopathology of measles infection in tissue culture will also be presented. The immunological studies include the neutralization of the measles virus in HeLa-cell cultures with distemper antiserum prepared by using the mouse-adapted as well as avian-adapted strains of distemper. Ferret protection tests in which ferrets have been immunized against measles and challenged with virulent distemper virus will also be reported, and,

Submitted for publication Feb. 12, 1958.

Read before the American Pediatric Society, Carmel, Calif., June 17-19, 1957.

Supported by Grant E-630 from National Institute of Health, U. S. P. H. S.

From the Departments of Pediatrics and Infectious Diseases, University of California School of Medicine at Los Angeles, and Veterans' Administration Hospital, Long Beach, Calif.

* Unpublished data. For a reference to FL cells see Fogh and Lund.[4]

finally, the neutralization of mouse-adapted distemper virus with specially prepared ferret measles antiserum will be detailed.

Material and Methods

The human measles pathological material was obtained from two patients who died of infection by measles virus. The first patient was studied at the Kern County General Hospital, Bakersfield, Calif., and the clinical and pathological data were supplied by Dr. R. W. Huntington. The second patient was studied at the Los Angeles Children's Hospital, and the case was made available by Dr. W. C. Thomas.† The details of these two patients were presented in a previous report[3] and will not be repeated here, except to state that the first patient was a 9-month-old white boy who died three days after admission to the hospital, with a pathological diagnosis of interstitial giant-cell pneumonia in association with a clinical diagnosis of typical measles (rubeola). The second patient was a white boy 5½ years old who died three days after being admitted to the hospital with a diagnosis of interstitial pneumonia. A diagnosis of measles had been made earlier, his sister being diagnosed as having measles at the same time.

Twenty-two susceptible ferrets were inoculated with the Lederle strain of ferret-adapted distemper virus; although varying doses were employed, the data reported here are from the animals which were given 100 MLD (minimum lethal dose). Animals were killed at various stages during their illness in order that the development of the pathologic changes might be studied. Seventeen additional ferrets were studied following infection with "hard-pad" distemper virus. The human tissues as well as the experimental ferret tissues were stained by picro-Mallory, hematoxylin and eosin, and hematoxylin and Shorr stains. The details of the modified picro-Mallory stain were presented in a previous paper.[3]

The Edmonston strain of measles virus was supplied to us by Dr. John F. Enders. It was successfully propagated and maintained in HeLa-cell cultures, which were then used in the neutralization studies which follow. The identity of the virus propagated in HeLa cells was established by means of neutralization and complement-fixation tests. The neutralization was carried out by mixing 200 TCD_{50} (tissue culture dose) of the viral tissue culture supernatant with dilutions of acute and convalescent serum from patients with typical measles. The mixtures were incubated at 37 C for one-half hour and at 4 C for an additional one-half hour before inoculation. Supernatant fluids from infected cultures were also employed as antigen for complement-fixation tests.

The avianized distemper virus was supplied by the Lederle Laboratories and was maintained by successive serial passage on the chorioallantoic (CA) membrane of 8- to 9-day-old chick embryos. Ten per cent suspensions of membrane in 1 ml. amounts were injected intraperitoneally into ferrets which were subsequently challenged with 100 MLD of virulent ferret distemper virus. The mouse-adapted distemper virus was developed by successive serial passage in brains of suckling mice from the egg-adapted strains. The LD_{50} of this virus after 45 passages in suckling mice is approximately $10^{-6.5}$, with an incubation period of four to five days. The 20% brain suspension from the 54th passage material was inoculated intraperitoneally into ferrets, which were subsequently challenged.

A medium containing 60% yeast extract medium,[11] 20% Scherer's maintenance solution,[12] 10% calf serum, and 10% brain-heart infusion broth was used to grow and maintain HeLa-cell cultures. The medium was changed every three or four days. Measles virus representing 200 TCD_{50} was mixed with equal amounts of diluted test sera and incubated at 37 C for one-half hour and placed in the refrigerator for an additional one-half hour prior to use. The standard inoculum was 0.2 ml. Observations in HeLa culture tubes were carried out for 21 days.

Eight ferrets were given two intramuscular injections of HeLa passage measles virus two weeks apart and were challenged two weeks later with approximately 100 MLD of virulent ferret distemper virus. In the second experiment five ferrets were given four intramuscular injections of measles virus at approximately three-week intervals, followed by a challenge three weeks after the final injection with approximately 50 MLD of virulent ferret distemper virus. In the third experiment seven ferrets were inoculated intramuscularly with 1 ml. of a mixture of measles virus and adjuvant. One additional inoculation without adjuvant was given approximately one month later, followed by a challenge with 100 MLD of virulent ferret distemper virus. Appropriate controls were carried along with each experiment and received normal tissue culture fluid instead of measles virus suspension.

In distemper neutralization studies equal amounts of mouse-adapted distemper virus and measles antiserum were incubated at 37 C for one-half hour and at 4 C for an additional one-half hour before injection of 0.01 ml. intracerebrally into suckling mice. All sera were inactivated at 56 C for one-half hour. The neutralization was determined by survival of the animals.

† Present address: Meadville City Hospital, Meadville, Pa.

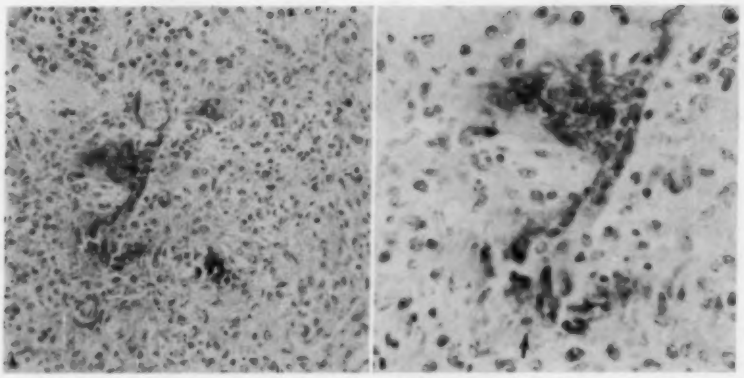


Fig. 1.—*A*, lung section from 9-month-old infant showing giant cell and interstitial pneumonia; reduced about 45% from mag. × 300. *B*, high-power view of the same giant cell to show cytoplasmic and intranuclear inclusion bodies; reduced about 45% from mag. × 700.

Results

In the first patient who died of interstitial pneumonia following measles, the gross examination of the thoracic cavity revealed obliteration of the right pleural space with numerous adhesions. The right and left lungs were similar, appearing to be completely consolidated. The microscopic study revealed a mononuclear cellular infiltration with fibrosis of the interstitial tissues. The alveolar epithelium was swollen and proliferative, and large giant cells were present throughout the alveolar areas. They contained nuclear as well as cytoplasmic inclusion bodies, which are illustrated in the accompanying photomicrographs (Fig. 1).

In the second patient the right and left lungs were firm and uncollapsing, moist, and pink with white markings following a lobular pattern on the pleural and cut surfaces. Both lungs had a firm hepatic feel and appearance. Microscopically the most striking finding was the occurrence of huge multinucleated cells, many of which contained up to 50 to 60 nuclei. The giant cells were found chiefly in the alveolar and bronchiolar lumens and appeared to rise from the lining tissue cells. In addition, the alveoli were filled primarily with an infiltrate of large mononuclear cells with reticulated nuclei. Eosinophilic inclusion bodies measuring 1μ to 5μ in diameter were

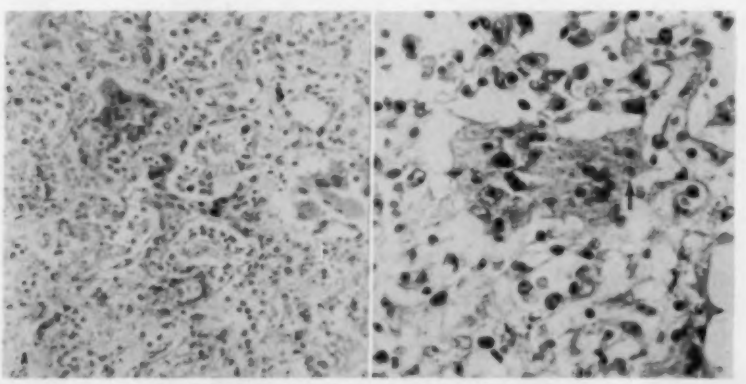


Fig. 2.—*A*, lung section from 5½-year-old child, showing giant cell and interstitial pneumonia; reduced about 45% from mag. × 300. *B*, high-power view of giant cell from the same child, showing cytoplasmic inclusion bodies; reduced about 45% from mag. × 700.

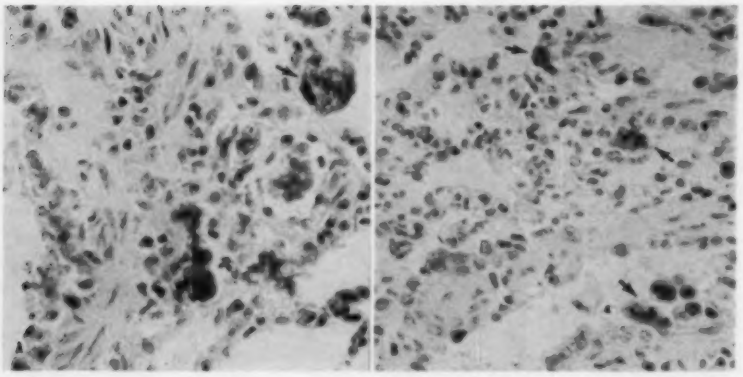


Fig. 3.—*A*, lung section from a ferret which died of distemper, showing several small giant cells and interstitial pneumonia; reduced about 45% from mag. × 700. *B*, lung section from a ferret which died of distemper, showing giant cells and interstitial pneumonia; reduced about 45% from mag. × 700.

seen in the cytoplasm of the alveolar and bronchiolar lining cells. Occasionally single cells and giant cells contained cytoplasmic inclusion bodies as well. These pathological changes are illustrated in Figure 2.

The most outstanding pathological finding in canine distemper as experimentally produced is the presence of cytoplasmic and intranuclear inclusion bodies in lung sections as well as in urinary sediment cells and in bladder sections. Inclusion bodies appeared as early as the ninth day after inoculation and were encountered primarily in the pharyngeal, tracheal, lung, bowel, and bladder tissues. Proliferative changes with giant-cell formation were evident 13 days after inoculation and are illustrated in Figure 3. Interstitial pneumonia with peribronchial involvement made up of infiltrated mononuclear cells and destruction of lining epithelium was a prominent finding in experimental distemper.[13] This was recorded clearly by De Monbreun,[14] who describes the inclusion bodies in the lung of dogs as follows: "In all cases cytoplasmic inclusion bodies were found in both bronchial and alveolar cells. In some bronchi they are especially abundant. They were situated in definite vacuoles and appeared well defined, usually round to oval, sometimes elongated.

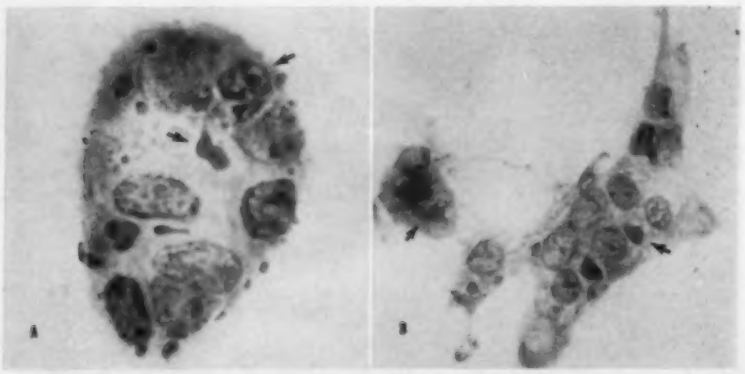


Fig. 4.—*A*, Warthin-Finkeldey cell from a child in preeruptive stage of measles, showing many cytoplasmic as well as intranuclear inclusion bodies reduced about 45% from mag. × 2200. *B*, typical Warthin-Finkeldey cell from a dog with distemper, showing many cytoplasmic inclusion bodies; reduced about 45% from mag. × 1350.

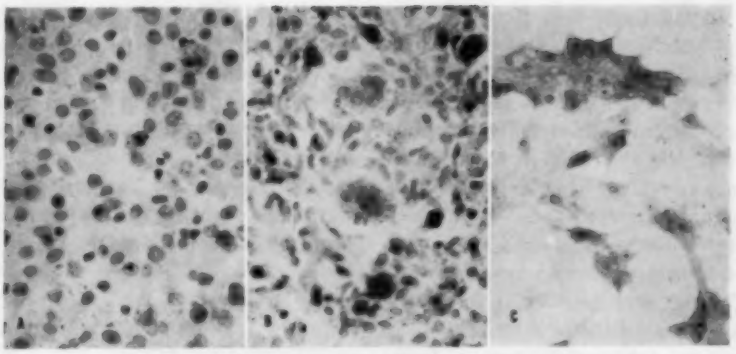


Fig. 5.—*A*, normal HeLa-cell tissue culture. *B*, photomicrograph of cytopathogenesis in HeLa-cell culture produced by measles virus, showing clumping of cells with giant-cell formation. *C*, FL cells (human amnion) infected with measles virus, showing typical spider-like changes with giant cell containing cytoplasmic inclusion bodies.

Vacuolated acidophilic bodies most often lie between the nucleus and the outer margin of the cell, but sometimes at the opposite poles of the cell." Warthin [15] and Finkeldey [16] described the occurrence of numerous large giant cells in tonsil and pharyngeal mucosa in the prodromal stage of measles. Similar cells have been found by pharyngeal smear biopsy from patients early in their illness with measles and in experimental distemper infection in ferrets. These giant cells contain characteristic cytoplasmic inclusion bodies when stained with the hematoxylin-and-Shorr and hematoxylin-and-eosin methods and are illustrated in the accompanying photomicrographs for comparison (Fig. 4).

The typical cytopathogenesis produced by measles virus in HeLa-cell cultures has been neutralized by both measles and distemper antiserums produced in ferrets. The cytopathology is characterized by a clumping together of cells, with spider-like filaments extending from the cells. Giant-cell formation is prominent, and many cells contain intranuclear as well as cytoplasmic inclusion bodies. These changes are illustrated in the accompanying photomicrographs showing normal HeLa cells and cytopathogenesis produced by measles virus in HeLa-cell cultures and in FL-cell cultures (Fig. 5).

In no case did the preimmunization or normal ferret serum show any inhibition of measles virus. The final titers of sera from ferrets immunized with distemper virus were of a low order, ranging from 1:2 to 1:16. A representative neutralization test was carried out by mixing 1:5 dilution of ferret serum with serial virus dilutions and showed that 2.5 L. $D._{50}$ of measles virus were neutralized by the serum from a ferret immunized with mouse-adapted distemper virus. When fresh normal guinea pig serum was employed as complement and added to ferret sera, the neutralization properties were enhanced, attaining levels of 1:16 and 1:128.

In the three experiments in which ferrets were immunized with measles virus by the methods outlined previously and subsequently challenged with distemper virus, some evidence of protection was evident, as revealed by prolonged incubation periods and modified illnesses with survival. Among the 20 experimental animals, 8 survived and 12 died, whereas only 1 animal survived the challenge among 17 controls. Serum from the one surviving control ferret which received only distemper virus showed a rise in measles antibody from 0 to 1:8.

Neutralization of the mouse-adapted distemper virus by specific measles antiserum prepared in the previous experiment was clearly demonstrated. When 300 LD_{50} of mouse-adapted distemper virus and undiluted measles antiserum mixtures were in-

oculated intracerebrally into 1- to 2-day-old mice, there was complete protection of the mice against the lethal effects of the virus. Preimmunization and control ferret serum showed no protective effect. Dilution studies revealed complete protection at 1:4. Similar protection was evident when antiserum produced by mouse-adapted and egg-adapted distemper virus was employed. When neutralization tests were carried out by mixing undiluted ferret sera with serial virus dilutions, 3200 L. D_{50} of distemper virus were neutralized by the serum from a ferret immunized with HeLa passage measles virus. When 100 LD_{50} of mouse-adapted distemper virus and sera obtained from acute and convalescent patients with measles were employed, significant increases in distemper-neutralizing substances were demonstrated in the sera of both patients. The details of these experiments were presented in a previous report.[17]

Complement-fixation tests on the paired sera of human subjects with measles and persons who were in contact with measles but who did not develop the disease are under study at the present time. Preliminary results reveal a fourfold or greater rise in titer in 12 of 16 patients. Both the early and late specimens were positive in three patients, and none of the specimens were negative. Anticomplement interfered with the test in one patient. Among the contact subjects, three revealed fourfold rises, in three others both specimens were positive, in three persons both specimens were negative, and in one the specimen was anticomplementary. The titer rise in patients with measles is higher than in the contact persons. This small study indicates that the test is satisfactory and reliable and suggests further that a few persons who are in contact with measles may have rises, the significance of which awaits further study.

Studies of 43 additional subjects with mild respiratory disease show 5 persons with rises in titer of fourfold or greater. In 15 persons both acute and convalescent titers were positive, with a mean acute titer of 1:32. The mean titer of persons who have recently recovered from measles is 1:128 in our series of 15 patients. This titer is identical with the mean titer reported recently by Ruckle and Rogers.[18] In contrast, they found that the mean titer of persons who have had measles a year or more previously is approximately 1:16.

Comment

Reference in the literature to the occurrence of characteristic giant cells in the lungs of infants dying after measles was first reported by Kromayer [19] and Hecht [20]; however, Denton [21] in 1925 and Pinkerton, Smiley, and Anderson [22] in 1945 called attention to the presence of inclusion bodies in the nucleus and cytoplasm of giant cells found in measles pneumonia. The latter authors also pointed out these same findings in canine distemper and suggested a close biological relationship between the two diseases. Experimental production of giant cells in lymphoid tissues with measles was accomplished by Gordon and Knighton [23] and Taniguchi et al.[24] Enders and Peebles [25] produced giant cells in tissue culture with human strains of measles virus. It is known that giant cells occur in a great many conditions, particularly chronic pulmonary diseases, but the formation of characteristic cytoplasmic as well as intranuclear inclusion bodies would not appear to be a common pathological finding except in measles and distemper. In both of the measles cases presented here these findings have again been pointed out and compared with the typical findings in distemper. The Warthin-Finkeldey cell has also been found and reported for the first time in canine distemper. The modified picro-Mallory stain and the hematoxylin-and-Shorr stains are particularly useful in demonstrating inclusion bodies in these tissues.

In this paper we have called attention to the clinical similarities, including a characteristic rash, as well as the similar epidemiological nature of these two diseases.

The incubation periods appear to be almost identical. Measles virus has recently been adapted to many different tissue culture preparations, but as yet the distemper virus has failed to grow in the same tissues. Both of these viruses, however, have been adapted to suckling mice in our laboratory, and cross neutralization studies are now in progress. Although it was demonstrated earlier that human serum was capable of neutralizing distemper infection in chick embryos and in ferrets,[13] we have pointed out here that human serum from patients recovering from measles will protect mice completely from death caused by distemper virus. Dr. Carlström,[20] in Sweden, has also established this same fact.

The cause of canine distemper was first considered viral in nature by Carré,[27] in 1905, and the disease is now referred to as Carré's disease. In 1926 Laidlaw and Dunkin [28] established the etiology to be a specific virus. In 1950 the immunologic and pathologic relationship was pointed out between canine distemper and respiratory disease of man at the Fifth International Congress of Pediatrics and subsequently published.[29-31] These studies have been confirmed by Karzon [32] and by Carlström.[8] The exact nature of the disease in man is still unknown, but the immunologic pattern appears to be similar to that recognized in many infectious diseases, with immunity in the newborn period, which decreases in a few months to negligible amounts and gradually increases again during childhood to adult levels which appear to be high and probably protective. In 1941 [31] one of us (J. M. A.) described a clinical disease entity, the pathology of which was subsequently shown to be similar to that of distemper. The disease primarily involved the respiratory passages, with the characteristic pathology occurring in these tissues. Prematurely born babies were highly susceptible, with a high mortality. This entity may represent the far end of the "clinical spectrum" of a common respiratory disease.

The correlation with measles (rubeola) would appear to be another step in the possible relationship, which will require more research into the various strains of measles and distemper plus further isolation attempts and correlations with clinical disease.

Summary

The pathologic and immunologic relationship of measles and distemper is supported by a descriptive comparison with photomicrographs and neutralization tests in tissue culture and animals. Mouse-adapted distemper virus infection in suckling mice is completely neutralized by specific measles (rubeola) antiserum from human and animal sources. The results suggest that common antigenic components are shared by the viruses of measles and distemper.

The photomicrographs were taken by Mr. Timothy Dodge.

Department of Pediatrics, University of California Medical Center (24).

REFERENCES

1. Adams, J. M.; Imagawa, D. T.; Yoshimori, M., and Huntington, R. W.: Giant Cell Pneumonia: Clinicopathologic and Experimental Studies, Pediatrics 18:888 (Dec.) 1956.

2. Black, F. L.; Reissing, M., and Melnick, J. L.: Propagation of Measles Virus in a Strain of Human Epidermoid Cancer Cells (Hep-2), Proc. Soc. Exper. Biol. & Med. 93:107 (Oct.) 1956.

3. Dekking, F., and McCarthy, K.: Propagation of Measles Virus in Human Carcinoma Cells, Proc. Soc. Exper. Biol. & Med. 93:1 (Oct.) 1956.

4. Fogh, J., and Lund, R. O.: Continuous Cultivation of Epithelial Cell Strain (FL) from Human Amniotic Membrane, Proc. Soc. Exper. Biol. & Med. 94:532 (March) 1957.

5. Ruckle, G.: Studies with Measles Virus: I. Propagation in Different Tissue Culture Systems, J. Immunol. 78:330, 1957.

6. Cabasso, V., and Cox, H. R.: Propagation of Canine Distemper Virus on the Chorio-Allantoic Membrane of Embryonated Hen Eggs, Proc. Soc. Exper. Biol. & Med. 71:246 (June) 1949.

7. Morse, H. G.; Chow, T. L., and Brandly, C. A.: Propagation of a Strain of Egg-Adapted Distemper Virus in Suckling Mice, Proc. Soc. Exper. Biol. & Med. 84:10 (Oct.) 1953.

8. Carlström, G.: Appearance in Children's Sera of Substances Capable of Neutralizing Canine Distemper Virus, Acta paediat. 45:180, 1956.

9. Yoshimori, M.: Unpublished, Thesis, University of California at Los Angeles, 1956.

10. Riazantzeva, N. E.: Experimental Measles in Puppies, Zhur. Mikrobiol., Epidemiol., Immunobiol. 27:5 (May) 1956.

11. Robertson, H. E.; Brunner, K. T., and Syverton, J. T.: Propagation in Vitro of Poliomyelitis Viruses: VII. pH Change of HeLa Cell Cultures for Assay, Proc. Soc. Exper. Biol. & Med. 88:119 (Jan.) 1955.

12. Scherer, W. F.: The Utilization of a Pure Strain of Mammalian Cells (EARLE) for the Cultivation of Viruses in Vitro: I. Multiplication of Pseudorabies and Herpes Simplex Viruses, Am. J. Path. 29:113 (Jan.-Feb.) 1953.

13. Adams, J. M.: Comparative Study of Canine Distemper and a Respiratory Disease of Man, Pediatrics 11:15 (Jan.) 1953.

14. De Monbreun, W. A.: Histopathology of Natural and Experimental Canine Distemper, Am. J. Path. 13:187 (March) 1937.

15. Warthin, A. S.: Occurrence of Numerous Large Giant Cells in the Tonsils and Pharyngeal Mucosa in the Prodromal Stage of Measles: Report of 4 Cases, Arch. Path. 11:864 (June) 1931.

16. Finkeldey, W.: Über Riesenzellbefunde in den Gaumenmandeln, zugleich ein Beitrag zur Histopathologie der Mandelveränderungen in Maserninkubationstadium, Arch. path. Anat. 281: 323, 1931.

17. Adams, J. M., and Imagawa, D. T.: Immunological Relationship Between Measles and Distemper Viruses, Proc. Soc. Exper. Biol. & Med. 96:240 (Oct.) 1957.

18. Ruckle, G., and Rogers, K. D.: Studies with Measles Virus: II. Isolation of Virus and Immunologic Studies in Persons Who Have Had the Natural Disease, J. Immunol. 78:341 (May) 1957.

19. Kromayer, E.: Über die sogenannte Katarrhalpneumonie nach Massern und Keuchhusten, Arch. path. Anat. 117:452, 1889.

20. Hecht, V.: Die Riesenzellenpneumonie im Kindesalter, eine historich-experimentelle Studie, Beitr. path. Anat. 48:263, 1910.

21. Denton, J.: Pathology of Fatal Measles, Am. J. M. Soc. 169:531 (April) 1925.

22. Pinkerton, H.; Smiley, W. L., and Anderson, W. A. D.: Giant Cell Pneumonia with Inclusions: A Lesion Common to Hecht's Disease, Distemper and Measles, Am. J. Path. 21:1 (Jan.) 1945.

23. Gordon, H., and Knighton, H. T.: Experimental Measles: Lymphoid Tissues of Animals Inoculated with the Virus of Human Measles, Am. J. Path. 17:165 (March) 1941.

24. Taniguchi, T.; Kamahora, J.; Kato, S., and Hagiwara, K.: Pathology in Monkeys Experimentally Infected with Measles Virus, M. J. Osaka Univ. 5:367, 1954.

25. Enders, J. F., and Peebles, T. C.: Propagation in Tissue Cultures of Cytopathogenic Agents from Patients with Measles, Proc. Soc. Exper. Biol. & Med. 86:277 (June) 1954.

26. Carlström, G.: Neutralization of Canine-Distemper Virus by Serum of Patients Convalescent from Measles, Letter to the Editor, Lancet 2:344 (Aug. 17) 1957.

27. Carré, H.: Sur la Maladie des jeunes chiens, Compt. rend. Acad. Sc. 140:689, 1905.

28. Laidlaw, P. P., and Dunkin, G. W.: Studies in Dog Distemper: Nature of Virus, J. Comp. Path. & Therap. 39:220, 1926.

29. Imagawa, D. T.; Yoshimori, M.; Wright, S. W., and Adams, J. M.: Serum Neutralization of Distemper Virus in Chick Embryos, Proc. Soc. Exper. Biol. & Med. 87:2 (Oct.) 1954.

30. Adams, J. M., and Imagawa, D. T.: The Relationship of Canine Distemper to Human Respiratory Disease, Pediat. Clin. North America 3:193 (Feb.) 1957.

31. Adams, J. M.: Primary Virus Pneumonitis with Cytoplasmic Inclusion Bodies: Study of Epidemic Involving 32 Infants, with 9 Deaths, J. A. M. A. 116:925 (March 8) 1941.

32. Karzon, D. T.: Studies on a Neutralizing Antibody Against Canine Distemper Virus Found in Man, Pediatrics 16:809 (Dec.) 1955.

Comparison Study: Silver Nitrate and Oxytetracycline in Newborn Eyes

A Comparison of the Incidence of Conjunctivitis Following the Instillation of Silver Nitrate or Oxytetracycline into the Eyes of Newborn Infants

PETER L. MATHIEU Jr., M.D., Providence, R. I.

Since the introduction of the Credé procedure for preventing ophthalmia neonatorum with silver nitrate, antibiotics have become available which are more effective than silver nitrate against both gonorrheal and other ocular infections common in the newborn infant.

The changing pattern of maternal infection since the advent of sulfonamides and penicillin has resulted in many localities in a reduction of gonorrheal infection with a relative increase in other pathogens. These changes are reflected in the kinds of ocular infections now seen in newborn infants. Staphylococcus species are now the commonest invaders, along with diphtheroid bacilli and coliform organisms, and at least two recent reports [1,2] fail to mention gonococci among the pathogens detected.

Penicillin and other antibiotics [1,3-5] have been shown to be adequate substitutes for silver nitrate, but the ability of penicillin to evoke sensitization reactions limits its value as a topical agent.[6] In view of the diversity of pathogens that may be encountered in neonatal conjunctivitis, it seems reasonable to assume that a broad-spectrum antibiotic might offer more satisfactory protection.

Oxytetracycline (Terramycin) was selected for trial as a substitute for silver nitrate, to be administered topically immediately after delivery. Oxytetracycline is effective against the great majority of organisms that cause neonatal conjunctivitis and has been used successfully in treating inclusion conjunctivitis.[7] Preliminary clinical reports [2,8] suggest that it is an effective prophylactic measure and that it does not irritate the eyes as does silver nitrate when it is administered topically. Tschan and Wright [9] have demonstrated that topical administration of oxytetracycline on the skin does not sensitize patients to subsequent systemic administration of the drug, and other studies [7,10] have shown that topical administration of oxytetracycline in the eye rarely if ever causes sensitization.

Materials and Methods

Observations were made on the eyes of 1139 infants deliverd at a large hospital between January, 1954, and May, 1955. Immediately after birth the eyes of each infant were washed with sterile saline solution and the excess fluid was wiped away with sterile cotton. Thereafter, one of three procedures was followed: (1) One drop of 2% silver nitrate was instilled into the inner canthus of each eye; (2) two drops of 0.5% oxytetracycline solution (Terramycin Ophthalmic Solution) were instilled into the inner canthus of each eye; (3) the left eye was treated with silver nitrate as in (1), while the right eye was treated with oxytetracycline as in (2). When silver nitrate was used, any excess was carefully wiped away with sterile cotton.

The eyes of each infant were examined daily during the first five days after birth for inflammation. The presence of any discharge of serous fluid, mucus, or pus was considered evidence of conjunctivitis and was classified so in the tabulations. A final report was obtained on almost all of the infants after six weeks, when they were seen in the well-baby clinic.

Submitted for publication Dec. 6, 1957.

The oxytetracycline (Terramycin Ophthalmic Solution) used in this study was supplied by the Medical Department, Pfizer Laboratories, Division of Chas. Pfizer & Company, Inc., Brooklyn.

Results

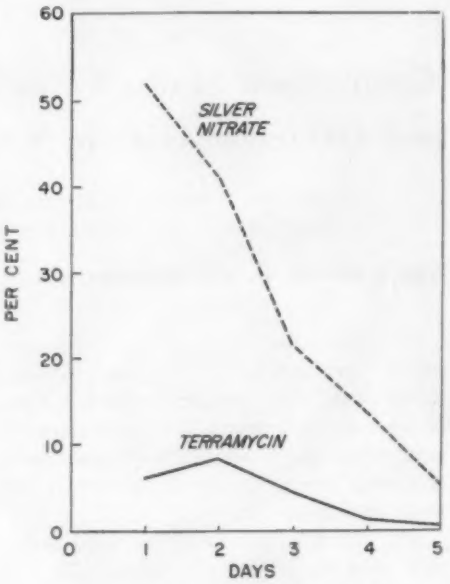
Of 106 infants given the conventional Credé treatment with 2% silver nitrate, a discharge was present with inflamed eyes or lids were swollen in 46% of the infants on the first day after instillation of the silver nitrate. The incidence decreased steadily through the fifth day, as shown in the table, to 6%, and no discharge remained in the eyes of any of the infants by the time of the examination after six weeks. Exudate was cultured from four of the six infants whose discharge persisted, but no organisms were detected.

The 908 infants given oxytetracycline, however, showed a much lower incidence of discharge throughout the first five days. The highest incidence (8.8%) occurred on the second day, and the incidence fell steadily to 0.4% on the fifth day. At the end of six weeks 846 of these babies were seen again, and none had any evidence of ophthalmic inflammation.

A third group of 125 infants was given oxytetracycline in the right eye while the left eye was treated with silver nitrate as a control. This procedure permitted a most rigorous comparison to be made between the two drugs. Here too, oxytetracycline was associated with a much lower incidence of inflammatory reactions, as indicated in the Table. In this group occurred the only instance of a frankly purulent discharge that was encountered in the entire study, in an eye in which silver nitrate was used. This infant was discharged with a very slight irritation and watery discharge from the left eye. One week later the eye was draining a thick yellowish pus, from which pneumococcal organisms were cultured. The other eye was inflamed, but no pus was observed. The infant was treated with oxytetracycline ophthalmic solution, 2 drops in each eye every three hours; both eyes were clear in about a week, and they were still clear at the time of the six-weeks' examination.

Incidence of Conjunctivitis

	Incidence of Conjunctivitis, %				
	Day 1	Day 2	Day 3	Day 4	Day 5
908 infants given oxytetracycline	5.9	8.8	4.3	1.0	0.4
106 infants given silver nitrate	46.0	34.9	15.1	14.7	5.7
125 infants given both					
Right eye (oxytetracycline)	4.8	2.4	3.2	0.8	0.8
Left eye (silver nitrate)	65.6	50.4	31.2	12.0	4.0



Incidence of inflammation.

The results in all 1139 infants are presented in graphic form in the Figure, which demonstrates the clear superiority of oxytetracycline to the Credé procedure in minimizing conjunctivitis.

Summary and Conclusions

A study of 1139 newborn infants was performed to compare the relative effectiveness of silver nitrate and topically applied oxytetracycline (Terramycin) in preventing conjunctivitis in newborn infants.

Gonorrheal ophthalmia is now much less frequent in many localities than infection by other organisms against which oxytetracycline is equally effective, and oxytetracycline does not produce chemical

conjunctivitis as does silver nitrate in a large proportion of cases.

Oxytetracycline was used alone in 908 infants; silver nitrate was used alone in 106, and in the remaining 125 infants oxytetracycline was used in one eye and silver nitrate, in the other.

No gonococcal infections were observed in many of the infants studied. The only frank infection in the entire series from which a pathogen could be recovered was observed in an eye treated with silver nitrate. This infection, from which pneumococcal organisms were recovered, responded to topical oxytetracycline therapy and was clear within a week.

While the absence of an untreated control group in this study prohibits any definite conclusion to be drawn regarding the effectiveness of oxytetracycline in preventing gonorrheal or other infections, it is clear that during the first five days infants given oxytetracycline showed a much lower incidence of conjunctivitis than did infants given silver nitrate, as measured by the presence of a discharge from the eyes: At some time during the first five days, 6% of those given oxytetracycline were affected, compared with 46% of those given silver nitrate.

255 Waterman St. (6).

REFERENCES

1. Allen, J. H., and Barrere, L. E.: Phophylaxis of Gonorrheal Ophthalmia of the Newborn, J. A. M. A. 141:522 (Oct. 22) 1949.

2. Kozinn, P. J.; Minsky, A., and Solomons, E.: Oxytetracycline Ophthalmic Solution in the Prophylaxis of Ophthalmia Neonatorum, in Antibiotics Annual 1955-1956, New York, Medical Encyclopedia, Inc., 1956, p. 307.

3. Davidson, H. H.; Hill, J. H., and Eastman, N. J.: Penicillin in the Prophylaxis of Ophthalmia Neonatorum, J. A. M. A. 145:1052 (April 7) 1951.

4. Franklin, H. C.: Prophylaxis Against Ophthalmia Neonatorum, J. A. M. A. 134:1230 (Aug. 9) 1947.

5. Watts, S. G., and Gleich, M. M.: Penicillin-Silver Nitrate Prophylaxis Against Gonorrheal Ophthalmia of the Newborn, J. A. M. A. 143:635 (June 17) 1950.

6. Welch, H.: Principles and Practice of Antibiotic Therapy, New York, Medical Encyclopedia, Inc., 1954, pp. 64-65.

7. Thygeson, P.: Terramycin in Ocular Infections, Tr. Am. Ophth. Soc. 49:185, 1952.

8. Willcockson, T. H., and Cox, C. D.: Bacteriological Studies in New Borns Using Terramycin, Terramycin-Polymyxin-B and Silver Nitrate, South Dakota J. Med. & Pharm. 6:147 (June) 1953.

9. Tschan, D. N., and Wright, C. S.: Safety of Systemic Oxytetracycline (Terramycin) Therapy Following or with Topical Therapy, A. M. A. Arch. Dermat. & Syph. 69:621 (May) 1954.

10. Town, A. E.: Ophthalmic Use of Terramycin, Am. J. Ophth. 34:723, 1951.

Twisted Hairs (Pili Torti)

A Pediatric Entity

SAMUEL J. NICHAMIN, M.D., Detroit

A rare congenital anomaly of the hair, occurring exclusively in the pediatric age group, has hitherto been regarded as solely within the province of the dermatologist. Although a definite clinical entity of childhood, it has received no precise description in pediatric periodicals or textbooks. This interesting anomaly of the hair, which is characterized by a twisting of each hair through 180 degrees along its long axis, is represented by less than 40 cases reported in the dermatologic literature. Additional cases would perhaps be reported were the clinical picture of the condition better known among those more immediately concerned with infants and children. Were pediatricians alert to the condition, a more accurate assessment of its frequency could be achieved. A case of pili torti from my private practice is herewith recorded in order to fulfill this desideratum.

Pili torti, the name of this rare malformation of the hair, in which tortuosities give it a corkscrew-like appearance, was first suggested by Ronchese.[1] The twisted hairs are short, broken, and of irregular shape. They have a dull and sparse appearance, in addition to being fragile or brittle. As a result, there develops a partial alopecia over the occiput, where there is maximum pressure and friction. The remainder of the scalp presents a lank and fuzzy aspect. The condition can thus often be diagnosed by gross examination and inspection. Microscopic study of the hair reveals a definite twisting or torsion at irregular intervals along the long axis, a phenomenon which is to be distinguished from actual beading.

Another characteristic feature is represented by a peculiar spangled glint, as light is reflected unequally from the twisted hairs. Occasional involvement of the eyebrows has been reported. The presence of twisting of the hair at birth has not been established. The condition becomes apparent as the hair develops during infancy, reaching its distinctive characteristics between 18 and 24 months of age. Girls are affected twice as often as boys.

Report of a Case

The patient was first seen at 2 years of age, on Dec. 16, 1955. The history revealed that the disturbance of hair growth was noted during the earliest months of infancy and became more apparent in the occipital area of the scalp at about one year of age. At birth it had been observed that she had a small circular lesion, about 2 cm. in diameter, located in the midvertex of the scalp, devoid of hair. This represented a sclerotic type of nevus, apparently unrelated to the abnormality of hair structure.

The birth and developmental history revealed no abnormalities. The birth weight was 6 lb. 7 oz. Cyanosis, jaundice, and convulsions were absent during the neonatal period. With respect to the family history, no relevant factors could be elicited. There had been no congenital malformations nor any abnormalities pertaining to hair growth or development. The parents were both in good health. There had been no miscarriages. No pertinent data were revealed with reference to hereditary diseases or stigmata, tuberculosis, allergy, diabetes, or convulsive disease.

Formula feedings, vitamins, and solid foods had been prescribed in the usual manner during infancy. The patient's nutritional progress had been unhampered by any food allergies, vomiting, or diarrhea. Routine immunizations were instituted during the first year. No severe illnesses had occurred

Received for publication Nov. 21, 1957.

From the Department of Pediatrics, Wayne State University College of Medicine, and the Children's Hospital of Michigan.

Figure 1

Fig. 1.—Posterior view of head of the patient, showing diffuse alopecia over the occiput. Above this area a round nevoid lesion is visible.

Figure 2

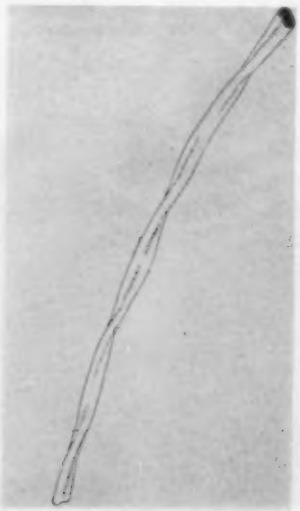
Fig. 2.—Hair of patient reported by Ronchese. (Reproduced by permission from Ronchese,[3] *Archives of Dermatology and Syphilology*, American Medical Association, Chicago.)

Transitory swellings at four to five months of age had led to a diagnosis of "mumps."

Except for the bizarre appearance of the hair over the occiput together with the above-mentioned nevoid lesion just cephalad, the child was a healthy-looking preschool youngster, with no other obvious abnormalities. Her height was 35 in.; weight, 30 lb. Skin coloring and nutritional state were within satisfactory limits. The four second deciduous molars were still unerupted. No abnormalities

Fig. 3.—Microscopic appearance of the hair shaft from the patient.

Fig. 4.—Drawing of hair shaft from the patient, showing the spiral twisting.



were found in the neck, chest, abdomen, extremities, and reflexes. The hemoglobin was 10.1 gm.; red blood cells, 3,890,000; white blood cells, 10,200, with polymorphonuclear cells, 37%, with 2% stab cells and 35% segmented forms; lymphocytes, 56%, and mononuclear cells, 7%. The protein-bound iodine was 5.1μg. per 100 cc. The urine examination was negative.

Over the occipital area of the scalp the hair was short, broken, kinky, and twisted, as well as very sparse. This condition of the hair can be readily ascertained from an inspection of Figure 1. In comparing this view of our patient's scalp with that of Dr. F. Ronchese's[1] case (Fig. 2), a striking similarity is apparent. Upon microscopic examination of the hair shaft, spiral twisting of the hair on its own axis was evident, as seen in Figure 3 and diagrammatically in Figure 4. A photograph of the microscopic appearance of the hair taken from another case of pili torti reported by Ronchese[2] demonstrated the same resemblance to a twisted rope. Beads or nodes, characteristic of monilethrix, are not present in this type of congenital abnormality of the hair. This serves as a differentiating point from the former condition.

The hair elsewhere on the patient's body, including the eyebrows, was normal. No parasites were found.

In the absence of satisfactory treatment for this abnormality of the hair, local symptomatic therapy was instituted, with use of a scalp lotion and a hydrous wool fat preparation. After several months of employment of these measures, no improvement in the condition of the hair was noticeable. During the ensuing summer of 1956 the child and her family spent their vacation on the Atlantic sea coast of Massachusetts. Subsequent to this exposure to the sun and air of the sea, the mother stated that there was a marked improvement in the growth and texture of the patient's hair, so that it practically covered the previous area of alopecia over the occiput (Fig. 5). However, the improvement proved to be only temporary, for with the onset of colder weather the former condition of the hair recurred. This course of events was duplicated in 1957. It is noteworthy that seasonal or climatic changes at home during previous years had produced no favorable effect on the condition of the scalp or hair. At the present time, although there are no visible areas of alopecia, the hair still presents gross abnormalities in length and texture. Because of the torsion of the hair shaft, in addition to its dryness and brittleness, the hair cannot grow to a desirable length.

Fig. 5.—Posterior view of head of the patient after a vacation at the seashore, showing regrowth of hair.

Comment

Partial alopecia about the occiput is commonly observed in the young infant whose position is primarily supine. Such a diffuse area of baldness would not necessarily incriminate the hair structure per se. With progressive postural development eliminating rubbing and friction of the back portions of the scalp, such bald areas gradually disappear. The hair finally presents a uniform growth over the entire scalp. Pili torti should be distinguished not only from the above-mentioned normal type of alopecia of early infancy but also from cases of monilethrix and trichonodosis. Microscopic examination of the hair with a low-power lens shows definite beading of the hair in monilethrix and knotting in trichonodosis, whereas a distinct twisting along the long axis of the hair and a peculiar corkscrew appearance characterize pili torti. Hellier[3] regards the prognosis of the latter to be more favorable than that of monilethrix. He states that only two definitely established cases of pili torti have been reported in adults. His observations tally with those of other authors, all of whom have noted that the hair becomes essentially normal after puberty.

In ringworm of the scalp, aside from circumscribed patches, there may be diffuse involvement of the hairs, especially in the occipital region, where maximum friction

from rubbing (as against the back of theater seats) occurs. Alopecia of the occiput resulting from this condition therefore requires differentiation from that caused by pili torti. Positive diagnosis of the former is made either by examination through a Wood's filter or by microscopic examination of extracted hairs, upon which spores may be found in abundance. These two conditions, interestingly, have in common a favorable prognostic relationship with puberty, in that both tend to disappear spontaneously during this period of development.

Clarke and Glicksberg [4] examined the hair follicles in cases of pili torti and found no pathologic changes of their intrinsic structure. Ronchese [1] noted that in his case the hairs of the occiput were more fragile than the hairs on the rest of the scalp, the average length being 1 to 4 cm. in the former region, and 10 to 12 cm. in the parietal region. In many of the reported cases scaling of the scalp has been noted, as well as ichthyosis in other parts of the body and in other members of the family. Ronchese [1,2] believes that there may be an impairment of the sebaceous glands, on an endocrine basis. In some reports an association has been noted with ectodermal dysplasia. Friederich and Seitz [5] report a case showing pili torti, dysplasia of the cornea, abnormality of the nares, and disturbances of sweat secretion.

No endocrine abnormalities were present in our patient. The concomitance of the nevoid lesion in the midvertex of the scalp referred to above and the condition of pili torti remains a point of interest and conjecture. Any significant relationship between the two would be difficult to establish. A complete endocrinological survey of our patient was not feasible. Since Ronchese [2] mentions a need for activating the thyroid gland in therapy, a protein-bound iodine estimation was done, with a result of 5.1 μg. per 100 cc., as noted above.

With local therapy of pili torti of doubtful value, other avenues of approach to amelioration of this malformation of the hair might be considered. The favorable outlook at puberty is not particularly comforting when one is confronted with the unsightly alopecia in a young child. It is to be noted that a rather dramatic improvement in the growth of hair over the previously bald occiput occurred in our patient subsequent to a complete change of environment. This represents a challenging approach for a therapeutic regimen based on climatic, and possibly psychogenic, factors. Further investigation and clarification are needed.

Summary

An anomaly of the hair, pili torti (twisted hairs), is described in a case report. As a well-defined pediatric clinical entity, it is deserving of consideration among the maladies of infancy and childhood. The hairs are fragile and are twisted on their own axes, with, in addition, a characteristic partial alopecia of the occiput. The phenomenon of the regrowth of hair in our case following environmental changes affords an area of investigation of the role of climatic or emotional factors in the pathogenesis of this disease.

Dr. James R. Rogin, Dr. E. W. Kelly, and Dr. Paul V. Woolley Jr. gave assistance in the preparation of this report.

672 Maccabees Bldg. (2).

REFERENCES

1. Ronchese, F.: Twisted Hairs (Pili Torti), Arch. Dermat. & Syph. 26:98-109 (July) 1932.

2. Ronchese, F.: Twisted Hairs (Pili Torti), Urol. & Cutan. Rev. 37:549-552 (Aug.) 1933.

3. Hellier, F. F.: A Case of Pili Torti: Clinical Description, Brit. J. Dermat. & Syph. 52:173-182 (June) 1940.

4. Clarke, G. E., and Glicksberg, E. L.: Pili Torti: Report of a Case, Arch. Dermat. & Syph. 43:836-838 (May) 1941.

5. Friederich, H. C., and Seitz, R.: A Form of Ectodermal Dysplasia, Showing Pili Torti, Ocular Manifestations, and Disturbance of Sweat Secretion, Dermat. Wchnschr. 131:277-283, 1955.

Thyroid Function in the Perinatal Period

DONALD E. PICKERING, M.D.; NICHOLAS E. KONTAXIS, M.D.; RALPH C. BENSON, M.D., and ROBERT J. MEECHAN, M.D., Portland, Ore.

Introduction

A better knowledge of thyroid function during the perinatal period should provide the basis for improved management of thyroid disorders of infants and should serve as a key to better understanding of the role of the thyroid gland in fetal growth and development.

Thyroid function during the perinatal period in mothers and infants, as indicated by serial variation in the concentration of serum butyl-extractable iodine (BEI), has not been wholly defined.[1-4] We have undertaken this study with use of a sensitive micromethod developed in our laboratory for the BEI determination.[5]

Studies to be presented include a series of BEI determinations on mothers and their progeny in the perinatal period and, in addition, supplemental studies of chemical and I^{131}-tracer analyses of thyroid glands in puppies. The latter studies were designed to elaborate specific features of thyroid hormone synthesis and release.

Methods

Clinical Study.—Duplicate serum BEI determinations were carried out on serial blood specimens obtained from a group of healthy women and their offspring during the last month of pregnancy, at the time of delivery, and at various intervals post partum.[6]

Submitted for publication Nov. 15, 1957.

Supported by U. S. P. H. S. Grant A-1296.

Presented before the Western Society for Pediatric Research, San Francisco, Oct. 29, 1957.

From the Pediatric Endocrine and Metabolic Research Unit, The Department of Pediatrics, and The Department of Biochemistry, University of Oregon Medical School. John and Mary R. Markle Scholar in Medical Science and Assistant Professor of Pediatrics, University of Oregon (Dr. Pickering).

Animal Study.—At birth, littermate puppies were given 20μc. of carrier-free I^{131} intraperitoneally, and these animals were killed at appropriate intervals. Their thyroid glands were removed, weighed, and homogenized. Following homogenization aliquots were taken for the following studies.

1. Tryptic hydrolysis was carried out according to the technique of Roche et al.[6] Thyroxin iodide * and thyroxin I^{131} were determined by a modification of the BEI method cited combined with the use of a scintillation counter for the I^{131} analyses.

2. Total thyroid iodide, total I^{131} content, and free thyroxin iodide were determined on aliquots of the nonhydrolyzed homogenate. The total iodide was determined by ashing a small quantity of the homogenate and then using the final step of the BEI procedure.

Results

Clinical.—Serum BEI values for mothers and infants are presented in Table 1.

Maternal predelivery BEI values shown represent specimens drawn during the last month of pregnancy. It will be noted from

* Thyroxin iodide refers to thyroxin-like compounds, chiefly thyroxin, but possibly also triiodothyronine.

TABLE 1.—*Butyl-Extractable Iodine Data for Mothers and Their Infants*

Group	Time	Cases, No.	BEI Value * (I⁻, μg./100 Cc.), Mean±S. D.
A. Mothers	Before delivery	10	5.8±1.1
B. Mothers	Labor	18	5.6±1.1
C. Mothers	4 days after delivery	26	5.8±1.2
D. Mothers	28 days after delivery	5	4.8±0.35
E. Infants	Birth (cord blood)	26	5.5±0.94
F. Infants	5 days	27	9.9±2.1
G. Infants	18–20 days	6	5.7±1.1
H. Infants	25–27 days	5	4.6±0.32
I. Infants	39+ days	5	6.5±1.0

Group Comparisons

Group B vs.	*P* Value	Group E vs.	*P* Value
A	>0.6	B	>0.7
C	>0.5	F	<0.001
D	>0.05<0.1	H	<0.05
--	--	I	<0.03

* Values shown represent serial specimens taken from a group of women during and following pregnancy and from their infants at birth and at ages indicated.

TABLE 2.—*Growth and Function of the Thyroid Gland in Puppies During the First Week of Life*

Animal No.	Age at Killing, Hr.	Body Wt. at Killing, Gm.	Thyroid Gland Analysis					
			Weight, Mg.	Total Iodide μg.	Free TxI⁻,* μg.	TxI⁻,† μg.	TxI¹³¹,‡	TxI¹³¹,§ Spec. Act.
1	12	198	28.2	15	0	2.0	50	25
2	24	237	30.4	20	0	3.0	54	18
3	60	330	45.4	29	0	4.5	46	10
4	180	755	98.2	61	0.27	12.0	39	3

* Free thyroxin iodide, determined on aliquots of the thyroid homogenates before hydrolysis.
† Thyroxin iodide, determined on aliquots of thyroid homogenates after enzymic hydrolysis.
‡ Thyroxin I^{131}, determined as per cent of total I^{131} trapped by the respective glands.
§ Specific activity of thyroxin represents the per cent of trapped I^{131} bound per microgram of thyroxin iodide.

the lower section of the Table (group comparisons) that there were no significant differences between maternal predelivery, labor, and fourth-postpartum-day specimens; however, specimens taken 28 days post partum showed a reduced BEI concentration of suggestive significance.

Infant cord blood serum BEI values did not differ from those of maternal sera obtained during labor ($P>0.7$), whereas by the fifth day of life the infants' serum BEI values had increased 80% over cord blood values ($P<0.001$). After the 5th day values declined, and they approached normal by 20 days of life.

Puppy Studies.—Data relating the growth of the thyroid gland to hormone synthesis and turnover during the initial 180 hours of life in puppies are presented in Table 2. Relationships between body weight, age, and thyroid weight and its functional components are subsequently presented graphically for discussion.

Comment

The similarity of BEI values in the infants' cord blood and maternal serum at the time of delivery observed in these studies is in keeping with previous reports.† These data indicate a free exchange of thyroxin across the placenta, as has been suggested by other studies.[7-10] In all probability, therefore, the corroboration of maternal-fetal BEI values exists well into early fetal life.

Though it has been established in several species, including humans, that the fetal thyroid gland is capable of function (the trapping of iodide and thyroxin synthesis) during the early part of gestation, it is not known if the fetus depends on its own thyroid gland for thyroid hormone.[8,11-14] The free transplacental passage of thyroxin must account for the apparent normalcy of most athyrotic human infants at birth and leads one to speculate that fetal thyroid function, while possible, is not essential to fetal growth and development.

It is of interest that despite the existence of similar serum BEI values in mothers and fetuses there exists a greater concentration of serum thyroxin-binding protein in maternal serum. That difference may well be important in augmenting the maternal-to-fetal transport of the thyroid hormone, since it is known that an increase in thyroxin-binding protein concentration is associated with a relatively greater per cent of total thyroxin being bound for transport and effectively acts to inhibit its uptake by tissues.[4,15]

Data pertaining to BEI values in mothers and their progeny following birth are graphically presented in Figure 1. The second point on the negative slope (12 to 14 days) of the curve showing infant values represents specimens not listed in Table 1.

During the period following delivery, there was but an insignificant change in maternal BEI values, whereas in infants, during the initial few days of life, a very

† Hormonal iodine values as determined by the BEI method employed in this study are lower than those reported in studies in which the protein-bound iodine (PBI) method has been used.[1-4] This is explained in part by the greater specificity of the BEI method for measuring thyroxin iodide alone.[5]

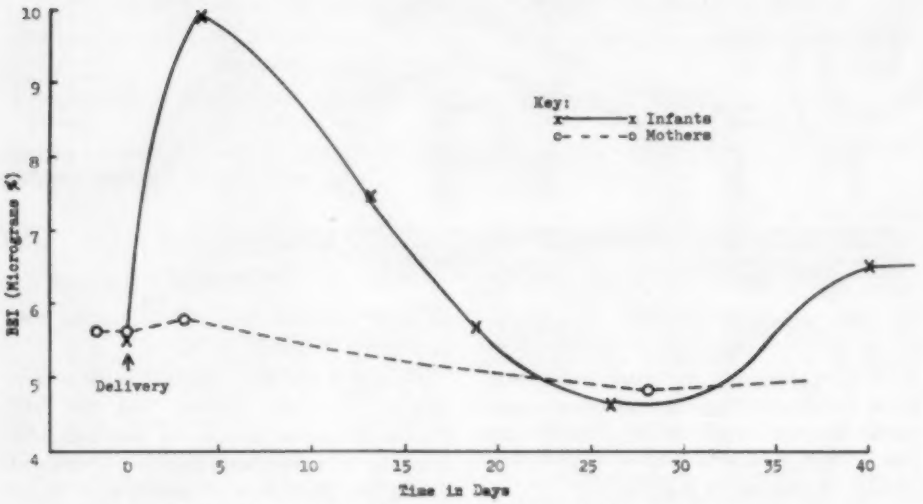


Fig. 1.—Perinatal serum BEI values in infants and their mothers.

significant rise in serum BEI concentrations was evident in all cases.

Because he observed an elevated thyroid I^{131} uptake in infants during this period, Van Middlesworth, being cognizant of the associated elevated serum hormonal iodine concentration, proposed that "the newborn infant may experience a period of physiological hyperthyroidism. . . . [as a result of] several possible mechanisms, i. e., (*a*) increased sensitivity of the thyroid gland to thyrotropic hormone, (*b*) increased production of thyrotropic hormone, or (*c*) complex alterations of endocrine balance." [16]

We have similarly observed an elevated 24-hour I^{131} uptake (60% to 70%) with administration of the isotope at birth. Of isotopic iodide trapped and retained by the gland at 24 hours, little or none was released to the circulation by the end of a 96-hour period of study. This suggests that whatever process is responsible for the accelerated uptake is not associated with a continuing increased rate of release of hormone by the gland.

In our laboratory we have repeatedly observed in studies of I^{131} uptake by thyroids of newborn monkeys that, whereas there is an increased uptake of I^{131} administered during the initial 24 to 48 hours of life (60% to 90%), the uptake of isotope administered after the age of 5 to 6 days is decreased. Thus, it appears that the elevation of BEI characteristic of the first few days of life leads to depression of I^{131} uptake, probably secondary to inhibition of pituitary thyrotropic hormone (TSH) release, and that, if the initially high uptake relates to increased TSH, the effect is short-lived. In one case in which serum BEI values were determined at frequent intervals during the initial 96 hours of life, it was observed that the maximal thyroxin-iodide (BEI) value was attained by 48 hours of age.

Thus, coincident to birth, there is released to the circulation a considerable quantity of thyroid hormone. In all probability the mechanism responsible for hormone release is short-lived and the function of the thyroid after 2 to 3 days of age is not associated with the release of significant amounts of hormone to the circulation until the age of 18 to 20 days, when serum BEI values approach normal. After the age of 25 days, when BEI values are lowest (4.6 ± 0.32), they rise and reach a plateau by 35 to 40 days, at a level of 6.5 ± 1.0.

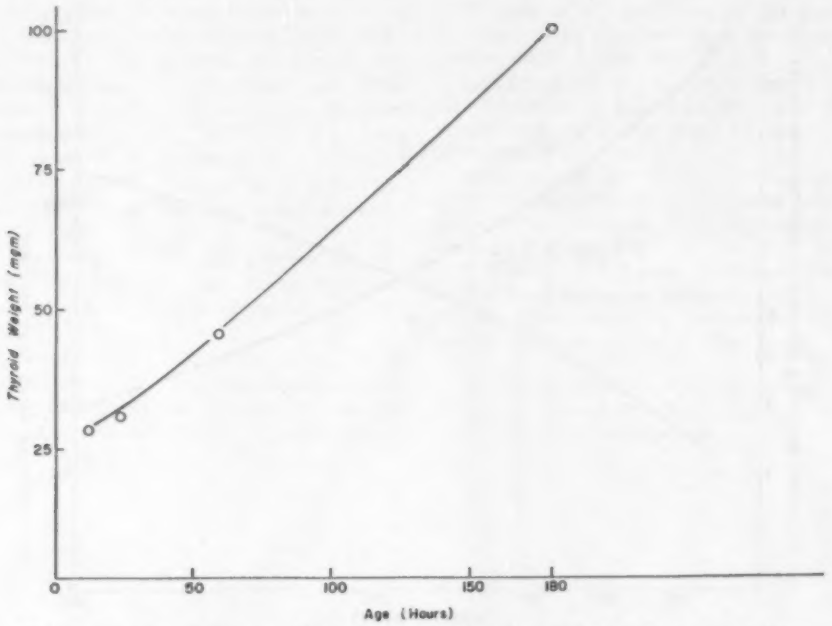


Fig. 2.—Growth of the thyroid gland in puppies during the first 180 hours of life.

Thyroid gland function, hormone production and release in particular, has been investigated in puppies through the initial 180 hours of their life. During that period there occurred a sizable increase in thyroid gland weight (30 to 90 mg.) and that increase paralleled age. (See Figure 2, and Table 3 which relate thyroid weight and age.)

It will also be noted in Figure 2 that there was constancy of the ratio of thyroid weight to body weight during this period, which implies that thyroid and general somatic growth were proportional.

TABLE 3.—*Relationships of Body Weight to Total Thyroid Weight and of Total Body Weight to Its Iodine and Thyroxin Content*

		Ratios		
Animal No.	Age at Killing, Hr.	Thyroid Wt. (Mg.) to Body Wt. (Mg.)	Total Iodide Content, (μg) to Thyroid Wt. (Mg.)	Thyroxin Iodide (μg.) to Total Iodide (μg.)
1	12	0.14	0.53	0.13
2	24	0.13	0.66	0.15
3	60	0.14	0.64	0.16
4	180	0.13	0.62	0.20

The total iodide content and thyroxin content of the glands increased with proportionality to the thyroid gland weight increment during the period, as is shown by the ratio of thyroxin iodide to total iodide. There occurred a proportionally greater increase in the thyroxin iodide than in the total iodide content of the gland.

Serial analysis of the specific activity of thyroxin iodide in the gland revealed a reduction which was nearly reciprocal to the increase in total thyroxin content.

Thus, by the marked increase in total thyroxin iodide content of the gland and the proportional reduction of the thyroxin specific activity, it is seen that there is a very active process of hormone synthesis which accommodates rapid thyroid gland growth during the initial 180 hours of life in puppies. There appears to be relatively little of this hormone released from the glands during this period. Such data support the preceding discussion concerning thyroid function in human infants during the neonatal period.

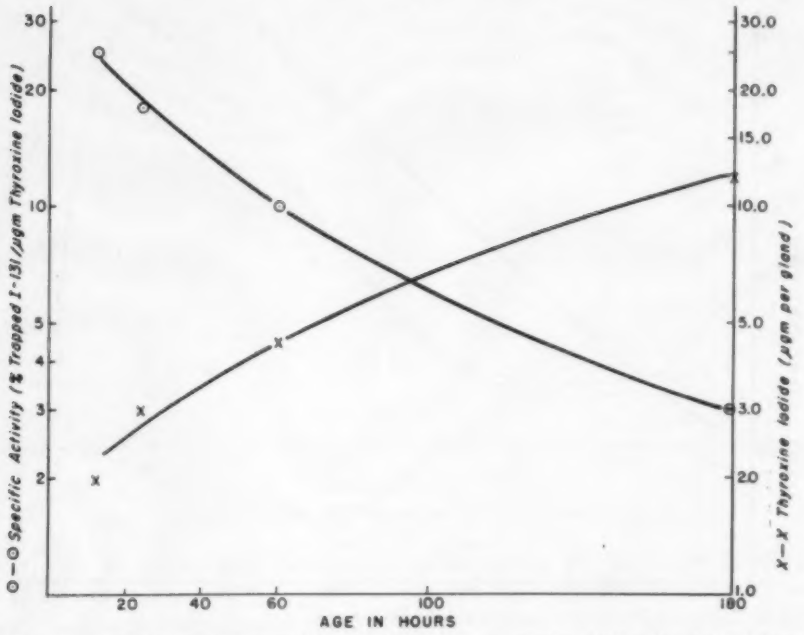


Fig. 3.—Thyroxin production and its specific activity in puppies during the first 180 hours of life.

Summary

Serial serum BEI concentrations were determined in approximately 25 mothers and their progeny during 30 days ante partum, at delivery, and at intervals during the first 40 days after delivery.

The BEI values in the mothers remained nearly constant throughout this period, and at delivery there was no significant difference between maternal and cord blood values: 5.6±1.1 versus 5.5±0.94μg. per 100 cc., respectively.

A sharp increase in the infants' BEI concentration occurred by the fifth day of life (9.9±2.1); thereafter their BEI values decreased, approaching normal by 18 to 20 days of age.

The significance of these data is discussed, in conjunction with supplemental studies of puppy thyroid gland function, with particular reference to hormone production and release by the thyroid gland during the early days of life.

Department of Pediatrics, 3181 S. W. Sam Jackson Park Rd.

REFERENCES

1. Danowski, T. S.; Johnston, S. Y.; Price, W. C.; McKelvy, M.; Stevenson, S. S., and McCluskey, E. R.: Protein-Bound Iodine in Infants from Birth to One Year of Age, Pediatrics 7:240, 1951.

2. Man, E. B.; Pickering, D. E.; Walker, J., and Cooke, R. E.: Butanol-Extractable Iodine in the Serum of Infants, Pediatrics 9:32, 1952.

3. Durham, J. R.; Cooke, R. E.; Lancaster, J. W., and Man, E. B.: Serum Butanol-Extractable Iodine Values of Children Under 10 Years of Age, A. M. A. Am. J. Dis. Child. 87:468, 1954.

4. Dowling, J. T.; Freinkel, N., and Ingbar, S. H.: Thyroxine-Binding by Sera of Pregnant Women, New-Born Infants, and Women with Spontaneous Abortion, J. Clin. Invest. 35:1263, 1956.

5. Kontaxis, N. E., and Pickering, D. E.: A New Micro-Method for Determining Butanol Extractable Iodine in Serum, to be published.

6. Roche, J.; Lissitzky, S., and Michel, R.: Chromatographic Analysis of Radioactive Iodine Compounds from the Thyroid Gland and Body Fluids, in Methods of Biochemical Analysis, edited by D. Glick, New York, Interscience Publishers, Inc., 1954, Vol. 1, p. 243.

7. Lybeck, H., and Hirvonen, L.: Studies of the Permeability of Guinea Pig Placenta to Radio-

active Iodine and Thyroxine Injected into a Foetus, Ann. Med. Exper. et Biol. Fenniae 34:129, 1956.

8. Jost, A.: The Secretory Activities of Fetal Endocrine Glands and Their Effect upon Target Organs, in Gestation: Transactions of the Third Conference, edited by C. A. Villee, New York, Josiah Macy, Jr. Foundation, 1956, p. 129.

9. Zondek, H.: On the Problem of Fetal Function of the Thyroid Gland, Acta med. scandinav. 103:351, 1940.

10. Grumbach, M. M., and Werner, S. C.: Transfer of Thyroid Hormone Across the Human Placenta at Term, J. Clin. Endocrinol. 16:1392, 1956.

11. Koneff, A. A.; Nichols, C. W., Jr.; Wolff, J., and Chaikoff, I. L.: The Fetal Bovine Thyroid: Morphogenesis as Related to Iodine Accumulation, Endocrinology 45:242, 1949.

12. Gorbman, A., and Evans, H. M.: Beginning of Function in the Thyroid of the Fetal Rat, Endocrinology 32:113, 1943.

13. Chapman, E. M.; Corner, G. W.; Robinson, D., and Evans, R. D.: The Collection of Radioactive Iodine by Human Fetal Thyroid, J. Clin. Endocrinol. 8:717, 1948.

14. Hodges, R. E.; Evans, T. C.; Bradbury, J. T., and Keetel, J. T.: Accumulation of Radioactive Iodine by Human Fetal Thyroids, J. Clin. Endocrinol. 15:661, 1955.

15. Freinkel, N.; Ingbar, S. H., and Dowling, J. T.: The Influence of Extracellular Thyroxine-Binding Protein upon the Accumulation of Thyroxine by Tissue Slices, J. Clin. Invest. 36:25, 1957.

16. Van Middlesworth, L.: Radioactive Iodide Uptake of Normal Newborn Infants, A. M. A. Am. J. Dis. Child. 88:439, 1954.

The Effect of a Corn Oil-Evaporated Milk Mixture on Serum Cholesterol Levels in Infancy

JULIUS POMERANZE, M.D.; ALTA GOALWIN, M.D., and LAWRENCE B. SLOBODY, M.D., New York

The group of substances known as the essential fatty acids (EFA) have recently become a central focus of research and interest in human nutrition. Of these linoleic, linolenic, and arachidonic are most commonly available in food and therefore of most practical importance. The original work with these acids, in dermatology, resulted in conflicting findings.[1-3] At the present, attention is concentrated on their role in relation to fat metabolism and consequently is directed toward their possible impact on atherosclerosis.

Sinclair[4] proposed that a disproportionate intake of saturated and unsaturated fats produces lipidemia through excessive esterification of cholesterol with saturated fatty acids, the products of which are not easily metabolized. It has been demonstrated in humans that high-vegetable-fat diets[5] and artificial diets containing corn oil[6] significantly lower serum cholesterol levels. The clinical importance of these findings resides in the at present enigmatic interrelationship between diet, cholesteremia, and atherosclerosis.

We determined to start work on this subject at the beginning, that is, in infants. At birth, the serum cholesterol level of an infant averages 75 mg. per 100 cc.[7] This level rises rapidly in the American child fed a cow's milk formula. However, during a serial study of serum cholesterol levels from birth, it was noted that infants fed a soy milk preparation because of an allergic state did not evidence the expected rise. The soy milk preparation is high in EFA. This observation was in agreement with the report of low cholesterol levels of infants in Italy, where infants are usually breast fed and early childhood diets largely contain vegetable fats.

A soy milk preparation and human breast milk contain a large amount of EFA. Cow's milk does not. Corn oil contains 53 gm. of linoleic acid, 12 gm. of saturated fatty acids, 28 gm. of oleic acid, and 1.5 gm. of sitosterol per 100 gm. We therefore decided to observe the effect of corn oil, added to an evaporated-milk formula, on serial serum cholesterol levels in infants.

Description of Sample and Methods

Three infants were followed on the pediatric wards of Metropolitan Hospital for a prolonged period. At the beginning of the study, two of the infants were receiving the usual evaporated-milk formula; the third, a soy milk. Fifty grams of corn oil was added to the evaporated milk formula in a homogeneous mixture obtained with a mechanical (Waring) blender. This formula was alternated with one of plain evaporated milk at the discretion of one of us (A. G.). Serum cholesterol levels were determined at weekly intervals on blood drawn from the femoral vein. To prevent a variable, no attempt to correlate results was made until the end of the study.

Each study terminated when an infant was discharged from the hospital. Then the serum cholesterol levels were equated with the feeding data.

Results

Figures 1, 2, and 3 indicate the apparent effect of the addition of corn oil to the evaporated milk on serum cholesterol levels. The administration of the mixture produced a rapid and sustained depression. When the corn oil was removed and the infant re-

Received for publication Dec. 28, 1957.

Supported by a grant from the Lipotropic Research Foundation.

From the Departments of Medicine and Pediatrics, New York Medical College-Metropolitan Medical Center.

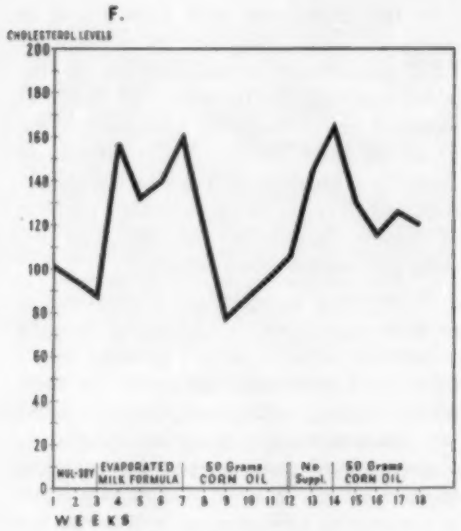


Fig. 1.—Subject 1.

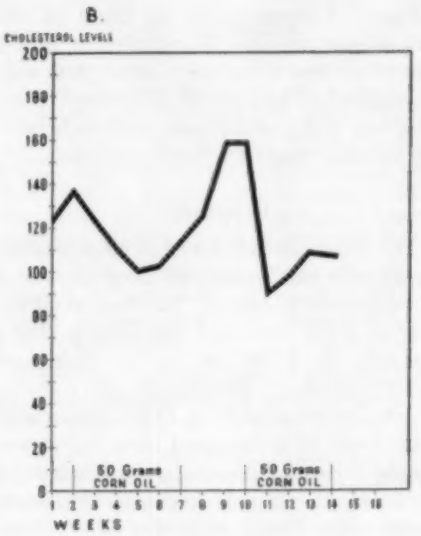


Fig. 2.—Subject 2.

turned to the usual evaporated milk formula, the cholesterol levels rose. Repeated feeding of the corn oil-evaporated milk mixture and its replacement by evaporated milk alone caused serum cholesterol levels to rise and fall in a predictable manner.

Figure 1 indicates the low serum cholesterol levels of the soy-milk-fed infant, which rose immediately when an evaporated milk formula was substituted. The addition of corn oil depressed the level of serum cholesterol, as in the other experiments.

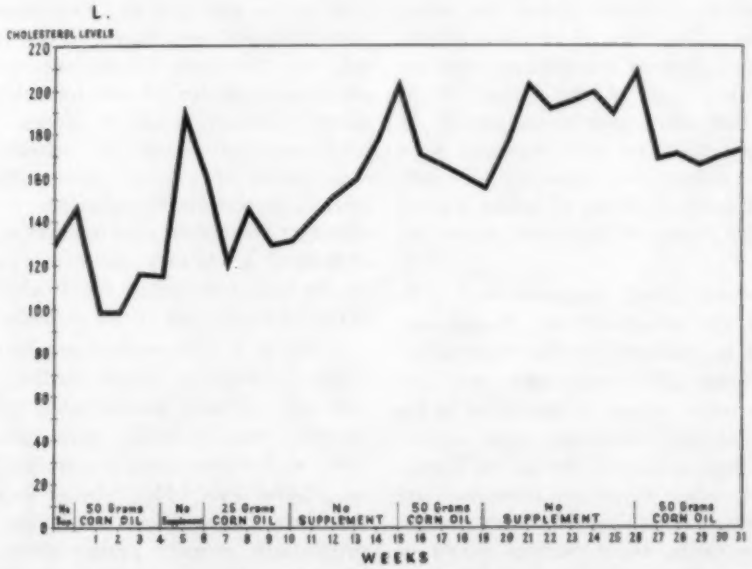


Fig. 3.—Subject 3.

Figure 3 demonstrates the effect of the corn oil-evaporated milk mixture on serum cholesterol levels of a third infant. Although the total effect of corn oil on serum cholesterol was a depressant one, with each cycle the baseline reached a higher plateau.

Comment

The results demonstrated in these experiments with infants parallel those of similar investigations in adults. The depressant effect of EFA and corn oil, with its large amounts of EFA, on serum cholesterol levels is obvious. Breast milk also contains a high percentage of EFA (53% unsaturated fatty acids, 47% saturated fatty acids) and should therefore depress serum cholesterol levels. Such an experiment is at present under way. Breast milk also differs from evaporated milk in protein and total fat content (1.2% protein in breast milk and 2.2% protein in evaporated milk diluted 1:2). In breast milk the protein is chiefly lactalbumin.

Evidence of atherosclerosis may appear as early as the age of 3 years, and, although remissions occur, the condition progresses as the person ages. The atherogenetic process is possibly reversible during the formative years. Therefore, if nutrition affects atherogenesis, it must be a constant influence over the life span of the person. It is possible that many nutritional aspects of infancy and childhood play prominent roles in the physiology and pathology of adulthood, not only by virtue of habits learned but also by metabolic alterations which are maintained.

Present-day efforts are concerned with reversing the atherosclerotic changes encountered in adulthood and averting malignant sequelae. But preventative medicine would be better served if alterations in the etiologic factors concerned with atherosclerosis were attempted during the formative years, when significant remissions are more easily accomplished. If dietary changes are to be made, these changes would be most useful if begun during early life.

In this experiment with infants and in others in adults, supplemental feeding of EFA presents a serious problem in the added calories. Fifty grams of corn oil increases tremendously the total daily caloric intake of these infants. It is difficult to reconcile a program to lower serum cholesterol and to create or aggravate the problem of obesity. Infants fed this additional formula gain weight more rapidly.

If we were to undertake a preventative program in infancy, one would be required to consider whether or not growing larger babies and probably larger adults by these added calories would not adversely affect our antidegeneration program by placing a greater burden on unadapted organs and biochemical mechanisms. Weight gain is not a measure of physiological well-being, nor does it insure the quality of growth.

An important practical problem is concerned with the stability of essential fatty acids. These are rapidly oxidized, and it is possible that in commercial preparations they quickly lose their efficacy. As a result, their administration would result in excessive calories without a decholesterolizing benefit.

It can be seen that this experiment suggests more problems than it solves. We can only say that corn oil in large amounts, added to an evaporated milk formula, lowers serum cholesterol levels in infants. It does not demonstrate that the attainment or maintenance of a lower serum cholesterol level is physiologically desirable. It is possible that the method used in lowering serum cholesterol levels may determine its value. In any case, a procedure which adds weight beyond the optimum is not valuable.

There is, as yet, no evidence for revolutionary changes in infant feeding. Cow's milk has not been demonstrated to be detrimental, but it would seem that breast milk, or formulae most resembling it, may be a better food. This type of experiment does not permit firm convictions for a prophylactic program against atherogenesis. However, diet does affect cholesteremia,

and, of the many atherogenic factors, nutrition is undoubtedly an important one which warrants study.

The interesting fact that a high intake of EFA lowers serum cholesterol levels in infants does not make the link between lipidemia and atherosclerosis clearer. Until a method more objective than biochemical is available for measurement of atherosclerosis in humans, epidemiologic studies will continue to give us inconclusive and conflicting answers to this important problem.

Conclusions

Fifty grams of corn oil added daily to an infant's evaporated milk formula significantly lowers serum cholesterol levels.

A physiologic advantage of this result has not been demonstrated.

Caloric excess associated with this type of experiment may be detrimental, since it encourages added weight gain.

If low serum cholesterol levels prove to be an advantage, breast milk or formulae resembling it may be the feeding of choice in infants.

2 5th Ave. (11).

REFERENCES

1. Hansen, A. E.: Serum Lipids in Eczema and in Other Pathologic Conditions, Am. J. Dis. Child. 53:933-946, 1937.

2. Ginsberg, J. E.; Bernstein, C., Jr., and Iob, L. V.: Effect of Oils Containing Unsaturated Fatty Acids on Patients with Dermatitis: with a Brief Report of an Experimental Study in Guinea-Pigs, Arch. Dermat. & Syph. 36:1033-1038, 1937.

3. Taub, S. J., and Zakon, S. J.: The Use of Unsaturated Fatty Acids in the Treatment of Eczema (Atopic Dermatitis, Neurodermatitis), J. A. M. A. 105:1675, 1935.

4. Sinclair, H. M.: Deficiency of Essential Fatty Acids and Atherosclerosis, Etcetera, Letters to the Editor, Lancet 1:381-383, 1956.

5. Groen, J.; Tjiong, B. K.; Kamminga, C. E., and Willebrands, A. F.: The Influence of Nutrition, Individuality, and Some Other Factors, Including Various Forms of Stress, on the Serum Cholesterol: An Experiment of 9 Months' Duration in 60 Normal Volunteers, Voeding 13:556-587, 1952.

6. Ahrens, E. H., Jr.; Blankenhorn, D. H., and Tsaltas, T. T.: Effect on Human Serum Lipids of Substituting Plant for Animal Fat in Diet, Proc. Soc. Exper. Biol. & Med. 86:872-878, 1954.

7. Pomeranze, J.; Goalwin, A., and Slobody, L. B.: To be published.

Meat in the Diet of Premature Infants

II. Influence on Red Cell Volume and Hemoglobin Mass

THOMAS R. C. SISSON, M.D., and LORRAINE E. WHALEN, Rochester, N. Y.

There is an almost inevitable development of anemia and iron deficiency in premature infants during the first year of life. Some observations [1,2] have suggested that the introduction of medicinal iron in early weeks of life will relieve part of the condition; other studies [3,4] have not supported this view.

It has been demonstrated that meat protein is as well absorbed and utilized as cow's milk protein by the premature infant,[5] and in the same study it was observed that the addition of meat to the diet resulted in a positive iron balance. An isocaloric milk diet did not. However, the measurement of iron balance presents disputable evidence because of its technical difficulties, and definite conclusions cannot be drawn from it.

The present investigation was undertaken to determine if meat would be an effective source of iron in the diet of premature infants. Experiments were planned to assess the influence of meat supplementation on the circulating hemoglobin mass, total red cell volume, and serum iron levels over the first year of life.

It was thought that these studies would provide a better evaluation than the simple measurement of hemoglobin concentration and hematocrit value.

Methods

Thirty-five premature infants in good condition, without hemolytic or other hematologic disease, and free of infection, were selected for serial observation. Twenty infants were controls, and fifteen were meat-fed. Nine additional controls were observed only once. Infants whose birth weights were below 1300 gm. or above 2300 gm. were excluded. Control and test subjects were alternated as they entered the premature unit from the delivery rooms of the institution. Twins included in the study were fraternal and, when selected, received identical diets, since it was impossible to be certain that only one would receive a meat supplement at home. When a set of twins was chosen, the next set was given the alternate diet.

Both control and test infants were given a half-skimmed milk formula (Alacta) while in the hospital. This diet provided 120 Cal. per kilogram per day, with 17% of the calories derived from protein. This permitted an intake of 5 gm. per kilogram per day from protein. When the infants were approximately 6 weeks of age an evaporated milk formula was substituted for the half-skimmed milk. This supplied a total caloric intake of 100 to 110 Cal. per kilogram per day, with 15% derived from protein. By the time of discharge the infants received 90 to 100 Cal. per kilogram per day. The control infants were given only this customary diet for premature infants.

The test subjects, in addition to the same diet, received a meat supplement.* This was begun between 2 and 4 weeks of age. At first, 10 gm. of meat was added to the day's formula. Five to seven days later, 30 gm. was added, and by the age of 6 weeks, 75 to 100 gm. After 8 weeks of age all the test subjects received 100 gm. of meat per day, and this supplement was maintained for the rest of the period of study. The basic half-skimmed milk diet was thus increased at first by approximately 1 gm. of protein and 1 gm. of fat. By the fourth or fifth week, the increase was about 3.5 gm. per kilogram per day, which gave a total protein intake of 21% to 22% of the caloric value. At the time of greatest increase in meat supplement (about 6 to 8 weeks of age) the infants were given the less calorically abundant evaporated milk formula. As the protein intake from milk was reduced the amount of protein from meat was

Submitted for publication Dec. 1, 1957.

Supported by a grant from Swift and Company.

From the Departments of Pediatrics, Obstetrics, and Gynecology of the University of Rochester School of Medicine and Dentistry.

* Swift's Strained Meats for Babies, supplied by Swift & Co., Chicago.

increased, so that an intake of 19% to 20% was maintained for four to six weeks. The test infants also had a higher caloric intake for this period, amounting to 120 to 140 Cal. per kilogram per day. This was in excess of requirements. It was estimated that the peak intake of protein in the meat-fed subjects was 6.5 gm. per kilogram per day, also in excess. No attempt was made to present isocaloric formulas to the two groups. This would have been simple during the hospital stay but a practical absurdity in the home for the many weeks of the study.

Cereal (fortified with iron by the manufacturer) and fruit was added to the diets of all the subjects between the third and fourth months of life. Vegetables and gelatin (Jello) were added the following month, and custards, soups, and egg yolk the month after that. A month later potatoes and, if development permitted, zweiback were given. The meat was fed to the test babies preferentially, and its bulk reduced the ingestion of other solids to some degree. It was not possible to measure the absolute intake of the different foods given. We were convinced, however, that the diets were comparable over the long period in both groups, except for the emphasis on meat in the test subjects.

The iron content of the diets without meat varied, but it was estimated from tables of nutritional analyses that the diets contained 4 to 10 mg. of iron per day. The amount absorbed is not known. Some investigations in adults and children[6,7] have demonstrated 10% to 13% absorption, greater than this in cases of iron deficiency. The meat supplement contained an average of 2.6 mg. of iron per 100 gm. by analysis.

After discharge from the premature unit the infants were examined in the pediatric outpatient department and occasionally at home for as long as contact with the families was maintained. An almost insurmountable obstacle in an investigation of this type is the loss of contact with some families before the study can be completed. For this reason, data are more complete for the early months. No difference existed between the groups regarding immunizations or other routines of pediatric care except that the control infants received no meat and the supplement of 100 gm. a day was maintained for the test group. The incidences of infection were the same for the two groups, except that two of the meat-fed group (Cases 13 and 14) also had varicella followed by rubeola with bronchitis. One other of that group (Case 10) had repair of bilateral inguinal hernias at the ages of 2 and 3 months. There was an average incidence of 1.5 upper respiratory infections per infant in each group. No infant escaped such illnesses.

It was impossible entirely to control the environment of the infants once they were at home, but assistance to the mothers was given by the visiting nurses and social service workers. All the babies studied were from similar marginal socioeconomic background, but of course the ancestral histories differed. It was our purpose to have the control and test groups as alike as possible, hoping that, as they enlarged, variations in background would tend to cancel out. This could be done with greater assurance only with a much larger series. It was realized that differences did exist which would not materially affect this study.

The following meats were used as supplements for the test group: liver, beef, pork, and lamb. The type of meat for each infant was changed about every month because of the slight variation of iron content. This resulted in a close similarity of the meat iron content in the over-all dietary intakes of the group.

All laboratory determinations were performed on venous blood samples. As it was necessary to repeat the observations, micro and semimicro techniques were employed. Repeated withdrawal of large volumes of blood would have induced anemia, invalidating the results. A total of 3.5 to 4.0 ml. of blood was taken at one time from a femoral vein. This was a sufficient sampling for the complete array of determinations.

Hemoglobin concentration was measured by the cyanmethemoglobin method of Crosby, Munn, and Furth.[8] Microhematocrits were determined by the use of an International Hemocrit Centrifuge. Plasma volumes were measured by a slight modification of the method of Nitsche and Cohen,[9] with use of Evans blue dye (T-1824), and by the elution of dye in acetone-water as described by Allen.[10] Recovery experiments yielded 97.0±2.0% dye on samples in triplicate. From these measurements were derived the values for total blood volume, red cell volume, and total circulating hemoglobin mass. In these calculations the factors for plasma trapped in the red cell column of the hematocrit tube[12,10] and for the ratio of body to venous hematocrit[10] were used. Total circulating hemoglobin mass was calculated from the total blood volume and hemoglobin concentration.

Slight modifications of the method of Burch, Lowry, and Bessey[14] for serum iron determinations and of the method of Rath and Finch[16] for measurement of the serum iron-binding capacity were used. Red blood cell and reticulocyte counts were done by the same experienced technician throughout the investigation, with use of the accepted methods for hematologic study.

Because of the differences in weights of the infants, results of volume and mass determinations are recorded in milliliters or grams per kilogram of body weight.

Summary of Data

Case	Sex	Total Observations, No.	No. of Observation	Birth Wt., Gm.	Age at Obs., Wk.	Wt. at Obs., Gm.	Hgb., Gm./100 Ml.	PCV, %	RBC ×10⁶	Plasma Volume, Ml./Kg.	Blood Volume, Ml./Kg.	Red Cell Volume, Ml./Kg.	Hgb. Mass, Gm./Kg.	Tot. Circ. Hgb. Mass, Gm.	Serum Fe Conc., μg./100 Ml.	Serum Fe Circ., μg./Kg.	LIBC,* μg./100 Ml.	Retic., %
Meat-fed infants																		
1	F	3	1	1,960	2 days	1,900	17.3	52.0	4.81	52.5	92.1	39.6	16.0	29.9	103	54	0	1.8
2	F	5	1	1,980	3 days	1,780	13.2	40.0	..	83.4	124.6	41.2	16.5	29.3	64	53	0	2.4
3	F	5	1	2,100	4 days	2,120	17.0	51.0	4.29	45.8	79.1	33.3	13.4	28.5	100	46	0	4.2
4	M	4	1	1,920	5 days	1,920	17.2	49.5	4.96	67.4	114.2	46.7	19.6	37.7	111	75	0	1.6
5	M	4	1	1,920	1.1	1,760	17.0	48.0	4.98	48.1	79.7	31.6	13.5	23.8	..	..	..	1.4
6	M	4	1	1,820	1.3	1,870	18.6	54.0	4.26	48.1	86.8	38.8	16.1	30.2	..	..	..	..
7	F	2	1	2,190	1.3	2,180	18.8	56.0	5.97	46.1	85.9	39.8	16.1	35.2	170	78	90	1.0
8	F	6	1	2,140	1.3	2,170	14.3	40.0	..	65.8	98.2	32.5	14.1	30.5	53	35	..	0.6
9	F	2	1	2,000	2.3	1,400	14.3	43.5	4.37	75.7	118.2	42.5	16.9	23.7	109	83	0	..
10	M	5	1	1,320	2.6	1,820	13.8	40.0	..	59.0	88.1	29.1	12.1	22.1	139	82	0	1.4
3	F	5	2	2,100	3.0	2,670	11.1	35.0	3.05	46.5	65.4	18.9	7.3	19.4	108	50	100	2.0
11	F	2	1	1,630	3.1	1,830	11.6	31.5	3.08	99.2	134.2	34.9	15.6	28.5	97	96	150	2.4
12	M	3	1	1,300	3.7	1,700	12.0	38.0	3.70	91.1	132.8	41.7	15.9	27.9	80	73	100	3.2
9	F	2	2	2,000	4.0	1,810	10.5	31.0	..	84.6	113.8	29.2	11.9	21.6	99	84	0	..
13	F	4	1	1,445	4.4	2,200	13.6	40.5	3.76	65.4	98.2	32.9	13.3	29.4	144	94	100	1.8
14	M	5	1	1,700	4.4	2,180	11.2	32.0	2.71	74.4	101.1	26.7	11.3	24.7	116	86	200	2.5
1	F	3	2	1,960	5.4	3,200	8.9	24.0	2.75	66.3	82.8	16.4	7.4	23.6	64	42	100	3.3
2	F	5	2	1,980	5.4	2,820	9.4	24.0	2.98	81.6	101.8	20.2	9.6	27.0	81	66	100	3.2
11	F	2	2	1,630	6.4	2,590	8.3	24.0	2.29	103.5	129.2	25.6	10.7	27.8	72	75	150	1.0
3	F	5	3	2,100	7.7	3,860	9.6	26.0	..	66.7	85.0	18.3	8.2	31.5	89	59	200	2.0
5	M	4	2	1,920	10.1	4,100	8.7	24.0	3.07	60.6	75.6	15.0	6.6	27.0	64	39	200	3.0
6	M	4	2	1,820	10.1	4,400	9.4	24.5	3.00	62.9	78.8	16.0	7.4	32.6	72	45	250	3.4
7	F	2	2	2,190	10.3	2,720	10.4	29.0	3.15	60.0	79.0	18.9	8.2	22.3	77	46	200	0.1
13	F	4	2	1,445	10.3	3,100	9.8	29.0	2.95	116.9	153.8	36.9	15.1	46.8	111	130	100	2.2
14	M	5	2	1,700	10.3	3,160	9.8	28.0	2.89	95.8	124.6	28.8	12.2	38.6	64	61	200	2.6
1	F	3	3	1,960	11.4	4,560	9.8	29.0	2.85	67.9	89.3	21.4	8.8	39.9	78	53	200	3.4
10	M	5	2	1,320	11.6	3,700	11.1	30.0	3.39	61.7	82.0	20.4	9.1	33.7	78	48	150	0.5
3	F	5	4	2,100	11.7	4,680	11.1	32.0	3.21	67.6	91.9	24.3	10.2	47.7	53	36	50	2.0
8	F	6	2	2,140	13.4	4,820	10.2	29.5	..	52.6	69.6	17.0	7.1	34.2	47	25	200	1.4
4	M	4	2	1,920	13.6	4,660	9.3	28.0	3.57	67.4	87.7	20.3	8.2	38.0	41	28	400	1.0
15	F	3	1	1,350	14.1	4,380	8.5	27.0	2.92	63.1	81.3	18.1	6.9	30.3	22	14	200	1.0
2	F	5	3	1,980	15.4	4,440	9.8	29.5	3.35	62.6	82.8	20.2	8.1	36.0	74	46	200	3.4
5	M	4	3	1,920	15.7	5,490	9.8	28.0	3.12	78.0	101.5	23.5	9.9	54.6	67	52	..	3.0
6	M	4	3	1,820	15.7	5,710	10.0	30.0	3.33	63.6	84.6	21.0	8.5	48.2	44	28	200	2.5
12	M	3	2	1,300	17.1	4,480	6.8	20.0	2.93	69.7	83.5	13.8	5.7	25.5	36	25	75	1.6
4	M	4	3	1,920	17.6	5,480	10.0	31.0	3.42	51.5	69.2	17.7	6.9	37.9	28	14	200	0.8
10	M	5	3	1,320	17.7	4,980	9.7	29.5	2.94	52.4	69.2	16.9	6.7	33.5	44	23	150	0.4
3	F	5	5	2,100	17.9	5,820	11.6	34.0	3.48	51.3	71.3	20.1	8.3	48.2	77	40	100	0.6
14	M	5	3	1,700	18.4	4,600	8.9	28.5	3.65	95.3	124.7	29.4	11.1	51.1	36	34	300	2.1
13	F	4	3	1,445	19.3	3,960	11.4	37.0	4.09	82.5	118.9	36.4	13.6	53.7	44	36	180	0.4
8	F	6	3	2,140	21.4	5,720	9.0	29.0	3.51	65.3	85.8	20.6	7.7	44.2	41	27	200	2.0
4	M	4	4	1,920	22.6	6,350	9.8	32.0	3.41	59.9	81.5	21.5	8.0	50.7	36	22	300	0.4
8	F	6	4	2,140	25.4	6,280	8.5	26.0	3.56	78.6	100.0	21.5	8.5	53.4	42	33	170	1.5
2	F	5	4	1,980	26.4	5,460	8.5	28.0	3.53	50.7	65.9	15.3	5.6	30.6	34	17	300	2.0
5	M	4	4	1,920	30.3	7,460	10.0	32.0	4.08	52.7	71.7	19.0	7.2	54.5	90	47	100	0.8
6	M	4	4	1,820	30.3	7,420	10.2	32.0	4.15	41.5	56.4	14.9	5.8	42.7	63	26	300	0.7
2	F	5	5	1,980	31.4	4,900	8.4	29.0	3.38	75.9	99.9	23.9	8.4	41.1	50	38	240	3.4
10	M	5	4	1,320	33.6	6,640	11.6	34.0	3.46	58.8	81.8	23.0	9.5	63.0	33	19	200	1.0
15	F	3	2	1,350	36.1	5,720	9.8	36.0	4.36	58.3	82.9	24.7	8.1	46.5	36	21	..	2.0
12	M	3	3	1,300	37.9	6,400	8.5	25.0	3.65	70.5	88.8	18.3	7.6	48.6	38	27	200	1.8
8	F	6	5	2,140	38.6	7,060	8.0	28.0	4.14	85.8	111.7	25.8	8.9	63.1	33	28	300	1.2
14	M	5	4	1,700	41.4	8,120	9.2	32.0	3.89	98.0	133.2	35.2	12.3	99.5	44	43	200	0.3
10	M	5	5	1,320	42.6	7,200	10.6	33.0	3.30	55.4	76.1	20.8	8.1	58.9	56	31	200	0.8
15	F	3	3	1,350	44.1	5,840	9.7	33.0	3.91	64.8	89.2	24.3	8.6	50.5	59	38	..	1.0
8	F	6	6	2,140	46.6	7,580	8.1	30.5	3.85	87.0	116.3	29.3	9.4	71.4	50	44	..	0.8
13	F	4	4	1,445	46.9	6,740	10.6	34.0	3.95	71.0	98.7	27.7	10.5	70.5	103	73	300	0.4
14	M	5	5	1,700	51.3	8,800	9.7	29.0	3.72	59.8	78.6	18.9	7.6	67.4	56	33	500	0.8

Control infants																		
16	F	2	1	2,000	2d	1,860	15.0	40.0	3.98	58.7	87.7	29.0	13.2	24.5	44	26	0	6.4
17	F	1	1	2,060	3d	1,980	16.2	47.0	4.84	70.1	114.5	44.5	18.5	36.7	67	47	0	7.4
18	F	2	1	1,930	4d	1,740	16.7	54.5	4.50	72.1	131.1	59.1	21.9	38.1	117	84	0	5.0
19	F	1	1	1,730	5d	1,740	18.8	49.0	4.47	59.7	100.3	40.6	18.9	32.8	153	91	0	3.4
20	F	5	1	2,300	5d	2,220	16.6	63.0	5.74	48.4	101.0	52.6	16.8	37.2	156	76	0	1.6
21	M	3	1	2,120	6d	2,330	15.8	45.0	4.20	54.2	86.2	32.1	13.6	31.7	111	60	--	1.0
22	M	4	1	2,240	6d	2,360	15.6	45.0	3.80	37.2	59.2	22.0	9.2	21.8	114	42	0	1.2
23	F	1	1	1,970	1.0	1,930	12.5	35.0	3.81	64.8	91.2	26.4	11.4	22.0	117	76	0	0.8
24	M	5	1	2,090	1.1	2,100	15.6	47.0	--	66.9	109.5	42.5	17.1	35.9	111	74	0	--
25	F	3	1	1,500	1.1	1,420	17.2	56.0	--	75.4	140.4	65.0	24.2	34.3	--	--	--	1.4
26	M	4	1	1,900	1.3	1,980	14.2	47.0	--	60.6	99.1	38.5	14.1	26.7	61	37	90	0.8
27	F	4	1	1,725	1.3	1,660	14.5	44.0	--	91.9	144.4	52.5	20.9	34.8	86	79	100	2.0
28	M	1	1	1,900	1.3	1,900	15.0	44.0	4.00	61.5	96.7	35.2	14.5	27.6	133	82	0	2.1
29	M	1	1	2,050	1.3	1,980	14.2	41.0	3.90	96.3	145.7	49.4	20.7	42.6	106	102	0	1.5
30	M	4	1	2,010	1.7	2,010	15.3	46.0	4.28	59.3	95.7	36.4	14.6	29.4	98	58	120	1.2
31	F	1	1	1,925	1.7	2,050	16.4	49.0	4.87	61.6	103.5	41.9	17.0	34.8	91	56	50	--
32	F	3	1	2,100	1.7	2,000	17.2	50.0	5.20	71.9	122.6	50.7	21.3	42.5	175	126	0	1.8
33	F	2	1	1,700	2.0	1,690	16.4	49.0	4.71	48.2	81.1	32.8	13.3	22.5	128	62	0	2.9
34	F	2	1	2,125	2.1	2,240	17.7	48.0	5.28	55.0	91.3	36.2	16.2	36.2	117	64	--	1.2
35	M	2	1	1,630	2.1	1,840	15.0	42.0	4.45	78.8	120.6	41.8	17.6	32.3	94	74	0	3.2
36	F	3	1	1,630	2.4	1,570	14.2	44.0	4.40	90.6	142.4	51.8	20.2	31.7	131	119	0	1.8
37	M	1	1	2,230	2.4	2,460	10.6	31.5	3.41	51.1	69.0	18.0	7.3	18.0	113	58	75	1.4
18	F	2	2	1,740	2.4	2,040	14.6	44.5	4.48	54.2	85.7	31.5	12.5	25.5	114	62	0	5.0
38	M	1	1	1,420	3.0	1,610	11.6	33.5	3.56	71.9	99.4	27.5	11.6	18.6	72	52	50	3.2
39	F	1	1	1,500	3.0	2,020	15.9	42.0	3.86	64.7	99.0	34.4	15.7	31.8	111	72	0	2.8
27	F	4	2	1,725	3.1	2,020	9.7	28.5	2.64	80.0	104.7	24.7	10.1	20.5	87	70	150	1.2
26	M	4	2	1,900	3.1	2,310	10.6	33.0	3.25	73.4	100.9	27.5	10.7	24.7	90	66	120	1.6
40	M	4	1	1,700	3.1	2,300	12.7	39.0	3.71	55.8	82.4	26.6	10.5	24.1	115	64	150	1.8
35	M	2	2	1,630	4.1	1,910	13.4	34.5	4.61	88.6	123.9	35.3	16.6	31.7	67	59	100	1.2
33	F	2	2	1,700	4.3	2,300	11.6	35.3	3.10	58.3	82.6	24.3	9.6	22.0	97	57	0	4.7
41	F	4	1	1,380	5.4	2,000	10.8	30.0	2.98	84.4	112.3	27.9	12.1	24.2	164	138	100	2.2
42	M	3	1	1,390	6.1	1,810	8.8	24.0	2.28	74.4	93.4	18.5	8.2	14.9	122	91	--	4.4
16	F	2	2	2,000	6.9	3,010	9.6	25.0	2.49	61.4	77.4	16.0	7.4	22.4	36	22	100	4.2
20	F	5	2	2,300	6.9	3,260	11.3	31.5	3.05	68.8	93.1	24.2	10.5	34.3	166	114	0	2.0
27	F	4	3	1,725	7.6	2,940	8.8	24.5	2.55	51.3	64.3	13.0	5.6	16.6	60	31	200	0.4
26	M	4	3	1,900	7.6	2,900	9.6	28.0	2.70	81.4	105.9	24.5	10.2	29.5	66	54	250	0.6
24	M	5	2	2,090	8.1	3,810	10.0	29.0	3.09	72.1	94.9	22.7	9.5	36.1	78	56	200	3.8
43	M	4	1	1,660	9.4	4,030	9.0	29.0	3.01	56.3	74.1	17.8	6.7	26.9	66	37	200	3.0
22	M	4	2	2,240	10.7	4,020	10.6	31.0	3.37	55.9	75.2	19.3	8.0	32.0	22	12	190	5.6
36	F	3	2	1,630	10.9	3,490	9.2	28.0	2.69	100.5	130.7	30.3	12.0	42.0	89	89	150	2.8
25	F	3	2	1,500	10.9	3,580	9.7	31.5	2.88	75.1	101.6	26.4	10.0	35.1	67	50	150	1.6
41	F	4	2	1,380	13.3	3,810	8.5	28.5	3.03	76.4	100.0	23.5	8.5	32.4	67	51	200	0.4
26	M	4	4	1,900	13.3	3,680	9.3	27.0	3.49	76.1	97.9	21.9	9.1	33.5	42	32	240	1.6
27	F	4	4	1,725	13.3	4,215	9.8	28.0	3.30	57.2	74.4	17.2	7.3	30.7	55	31	200	1.2
22	M	4	3	2,240	14.7	4,720	10.6	32.0	3.29	54.6	74.2	19.6	7.9	37.1	42	23	165	0.4
20	F	5	3	2,300	14.9	4,520	10.9	26.0	--	51.2	65.2	14.0	7.1	32.1	58	30	50	--
34	F	2	2	2,125	15.3	3,440	9.9	28.5	--	46.0	60.1	14.2	6.0	48.7	--	--	--	1.2
21	M	3	2	2,120	15.4	5,660	11.9	33.0	3.21	65.5	90.1	24.6	10.7	60.7	97	64	--	0.2
44	M	3	1	1,300	15.7	4,660	9.7	27.0	2.53	40.8	52.5	11.7	5.1	23.7	61	25	160	1.2
41†	F	4	3	1,380	16.0	4,140	8.3	24.0	3.05	95.4	119.0	23.6	9.9	40.9	59	56	200	0.2
43	M	4	2	1,660	16.4	4,470	10.4	31.0	3.44	64.5	86.8	22.2	9.0	58.4	36	23	200	0.5
32	F	3	2	2,100	16.6	5,020	11.6	33.0	--	55.1	75.8	20.7	8.8	44.1	42	23	--	1.6
42	M	3	2	1,390	20.3	4,320	7.7	28.0	3.76	44.6	58.1	13.4	4.5	19.2	29	13	410	3.6
43	M	4	3	1,660	20.4	5,540	9.8	32.0	3.75	53.5	72.8	19.2	7.1	39.5	50	27	250	0.3
20	F	5	4	2,300	22.9	5,750	12.0	36.0	3.59	56.3	80.1	23.8	9.6	55.3	88	50	150	2.6
21	M	3	3	2,120	28.4	7,560	11.5	34.0	3.77	50.9	70.8	19.9	8.1	61.5	83	42	--	0.6
44	M	3	2	1,300	28.7	5,360	8.3	27.0	3.54	59.7	76.9	17.2	6.4	34.2	33	20	190	0.9
32	F	3	3	2,100	28.9	7,900	10.7	30.5	4.40	51.7	69.1	17.4	7.4	58.4	41	21	200	1.2
40	M	4	2	1,700	30.0	5,410	7.6	27.0	3.24	48.9	62.9	14.0	4.8	25.9	33	16	200	--
41†	F	4	4	1,380	30.3	7,300	9.7	30.0	4.25	69.0	91.8	22.8	8.9	65.0	20	14	250	0.4
24	M	5	3	2,090	32.0	7,600	5.9	27.0	3.88	48.1	62.0	13.8	3.7	27.8	26	13	420	2.4
22	M	4	4	2,240	34.7	6,960	5.6	22.0	3.64	70.9	86.6	15.7	4.9	33.8	44	31	250	0.4
40‡	M	4	3	1,700	35.4	6,680	11.0	34.0	3.28	59.3	82.5	23.2	9.1	60.6	--	--	--	--
43	M	4	4	1,660	36.1	7,460	7.3	26.5	3.25	44.5	57.0	12.5	4.2	31.1	33	15	200	1.2
42‡	M	3	3	1,390	36.3	7,000	11.8	27.0	4.19	72.1	92.9	20.7	11.0	75.6	75	54	96	--

Summary of Data—Continued

Case	Sex	Total Observations, No.	No. of Observation	Birth Wt., Gm.	Age at Obs., Wk.	Wt. at Obs., Gm.	Hgb., Gm./100 Ml.	PCV, %	RBC $\times 10^6$	Plasma Volume, Ml./Kg.	Blood Volume, Ml./Kg.	Red Cell Volume, Ml./Kg.	Hgb. Mass, Gm./Kg.	Tot. Circ. Hgb. Mass, Gm.	Serum Fe Conc., μg./100 Ml.	Serum Fe Circ., μg./Kg.	LIBC,* μg./100 Ml.	Retic., %
41	M	3	1	1,300	36.7	6,020	7.2	29.0	4.36	77.6	102.1	24.5	7.3	44.2	38	29	100	0.3
96	F	3	2	1,650	40.0	7,000	6.3	23.0	3.27	82.2	101.5	19.3	6.4	44.8	11	9	--	0.6
25	F	3	3	1,500	40.0	7,200	6.8	24.0	3.56	74.9	93.5	18.5	6.4	46.4	23	17	--	1.0
24	M	6	4	2,090	46.0	8,960	5.0	19.0	3.98	61.5	72.9	11.5	3.6	32.7	34	21	330	2.3
39	M	4	2	2,010	40.6	9,180	6.7	27.0	4.51	49.8	64.2	14.3	4.3	39.5	17	8	400	0.3
40†	M	4	4	1,700	47.4	8,200	12.0	33.0	--	56.9	80.1	23.2	9.6	78.8	56	32	170	0.8
20	F	5	5	2,300	46.9	7,880	10.6	30.0	3.40	53.4	73.6	18.3	7.8	61.5	44	24	150	0.6
36	M	4	3	2,010	50.6	9,250	5.8	23.0	--	57.3	70.8	13.4	4.1	38.0	17	10	450	0.3
28†	M	5	5	2,090	51.1	9,540	8.9	36.0	5.09	43.4	57.7	14.3	5.1	49.0	--	--	--	3.7
30‡	M	4	4	2,010	52.0	9,300	10.3	32.0	4.32	62.2	84.6	22.4	8.7	81.0	28	17	320	1.0

* Latent iron-binding capacity.
† Treated with ferrous sulfate (12.5 mg. of elemental iron per day).
‡ Treated with 400 mg. of iron-dextran given intramuscularly.

Results

The results obtained for each infant are listed by age at time of test and by group in the Table.

A. Hemoglobin Concentration.—The customary fall of hemoglobin concentration seen in all premature infants occurred in the subjects of this study. It was similar in the two groups until about 8 weeks of age. At that time a rise of concentration took place in the meat-fed infants that was sustained until 16 to 18 weeks. An elevation did not appear in the control group until 12 to 16 weeks, if at all.

After the 20th week the rise in hemoglobin concentration in the meat-fed group leveled off, then partially subsided. At about the 28th week a second rise in concentration occurred and persisted for the rest of the year.

Previous levels of hemoglobin concentration were not maintained in the controls after the 20th week and followed a steady decline until the end of the study. It is well to note that the higher values in the control group after 20 weeks of age were found in infants given oral or parenteral iron therapy.†

B. Packed Red Cell Volume.—There was an initial decline of hematocrit in both groups of infants. A rise occurred in the meat-fed group at about the 10th week; this rise did not appear until the 15th to 16th week in the controls. After this a gradual fall was seen in both groups. At about the 30th week, however, there was an increase of hematocrit in the meat-fed infants, though the hematocrit continued to decrease in the controls.

C. Total Blood Volume.—There was a wide range of values for blood volume in

† Iron was administered orally as elixir of ferrous sulfate (12.5 mg. per day of elemental iron) for a minimum of three months. Iron was administered intramuscularly in a total dose of 400 mg. (Imferon, supplied by Dr. H. L. Daiell, Medical Director of the Lakeside Laboratories, Milwaukee). These iron preparations were given because it was believed necessary for the health of the infants.

both groups from birth through the first year of life. There was a gradual mean fall from 105 ml. per kilogram in the first week to a level of 85 ml. per kilogram in the eighth week. This value was maintained until the 14th week, when a level of 75 ml. per kilogram was reached. This stabilized until the 30th week, when a rise to a mean of 82 ml. per kilogram was noted. This value held through the rest of the year. This obtained for both groups, with no significant difference between the two.

D. Plasma Volume.—The mean plasma volume ranged from 55 to 76 ml. per kilogram through the first year of life in both groups, with no significant trend at any time. There was no apparent trend in any individual subject. The plasma volume appears to be an independent component of the blood, which alters to maintain the total blood volume as need arises.

E. Total Red Cell Volume.—There was a rapid fall of red cell volume in the control group during the first four to six weeks. A more gradual decline progressed to the 10th week. This was accelerated to the 18th to 20th weeks, and then a slow rate of fall continued for the rest of the year. Only one of the control infants achieved an increase of red cell volume without the impetus of iron therapy.

The controls, in short, demonstrated at first a marked, rapid fall of red cell volume and then a continued though slower decline. In general they were unable to maintain the level reached at 6 weeks of age without the administration of medicinal iron.

A different sequence of events occurred in the meat-fed group. The same rapid and profound fall of red cell volume was found in these infants as would be expected, with a similar, and in some instances sharper, decline to about the eighth week. At this time all but three of the test subjects had a temporary increase of red cell volume, whereas only one of the control infants had such an increase. Subsequent reduction of red cell volume in the meat-fed infants was

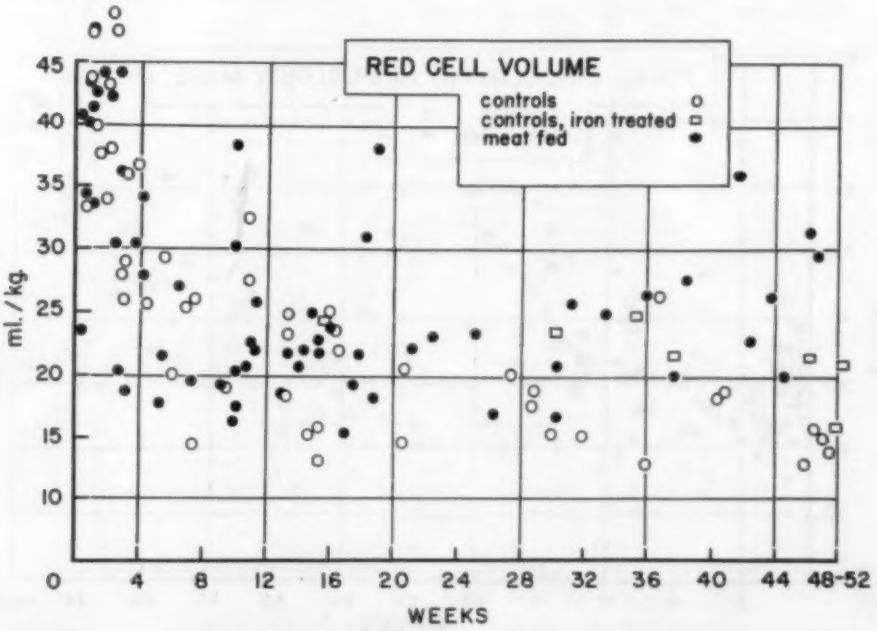


Fig. 1.—The red cell volume of both control and meat-fed infants in milliliters per kilogram of body weight during the first year of life.

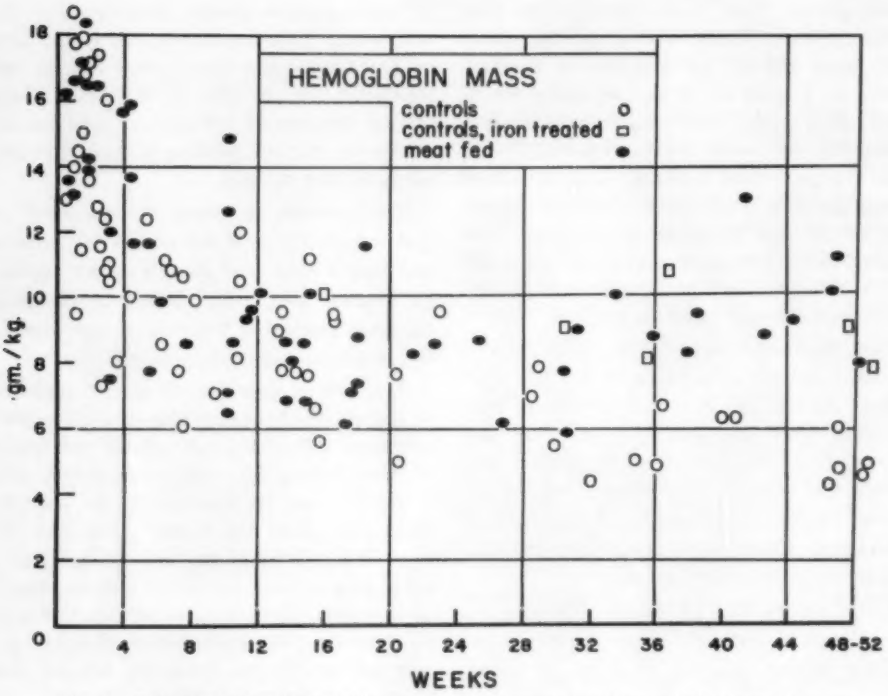


Fig. 2.—The circulating hemoglobin mass of both control and meat-fed infants in grams per kilogram of body weight during the first year of life.

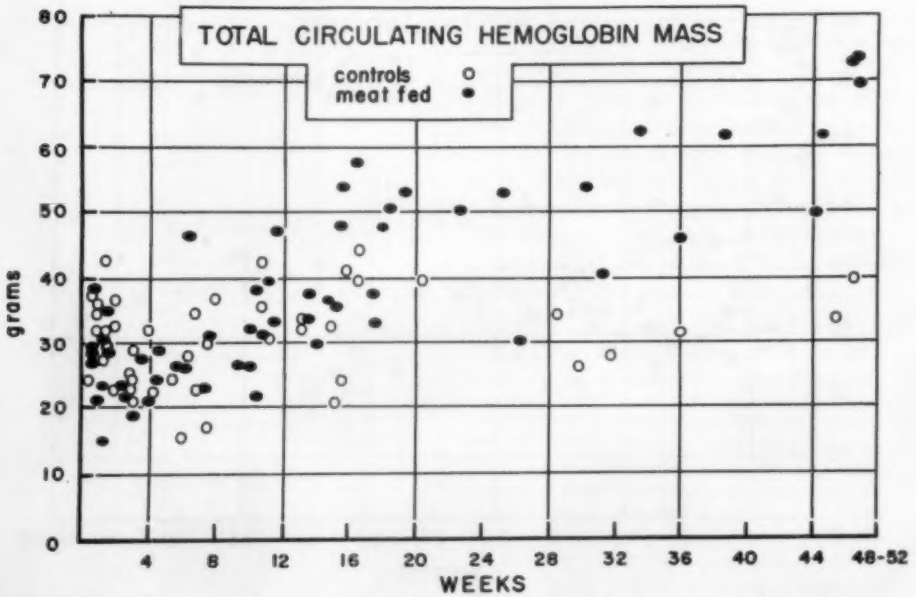


Fig. 3.—The total circulating hemoglobin mass of both control and meat-fed infants during the first year of life, not based on body weight.

small. The values were generally higher than those of the controls between the 16th and 30th weeks. It may be noted that between 28 and 30 weeks of age the red cell volumes of the test group tended to increase, and by the end of the year these values were significantly higher than those of the controls.

F. Total Circulating Hemoglobin Mass.—There was a rapid fall of circulating hemoglobin mass in the group of control infants in the first 6 weeks, a substantial though less abrupt fall to the 10th week, and then a gradual and sustained decline to the end of the period of study.

An initial reduction of hemoglobin mass was found in the meat-fed infants. This downward trend, with but three exceptions, was reversed between the sixth and eighth weeks. The mass was generally well maintained in this group to the 28th to 30th weeks. From that point on there was an increase of hemoglobin mass which was not duplicated in the control group of infants.

Figure 3 illustrates the total circulating hemoglobin mass values (not calculated on the basis of body weight) that were encountered in the infants of both groups.

The mean circulating mass of the controls did not return to the value of the 1st week of life until the 12th week. This return occurred about the eighth week in the meat-fed group. The gradual increase in total mass which should logically accrue in all these infants with growth was minimal in the controls throughout the entire period of study and, indeed, did not reach the values of the meat-fed infants after the 16th week.

G. Serum Iron.—With but two exceptions, the serum iron levels of the control group fell throughout the first year of life. The serum iron values of the meat-fed group decreased until the 16th week and then leveled off or rose only slightly until about the 30th week, after which there was a distinct increase.

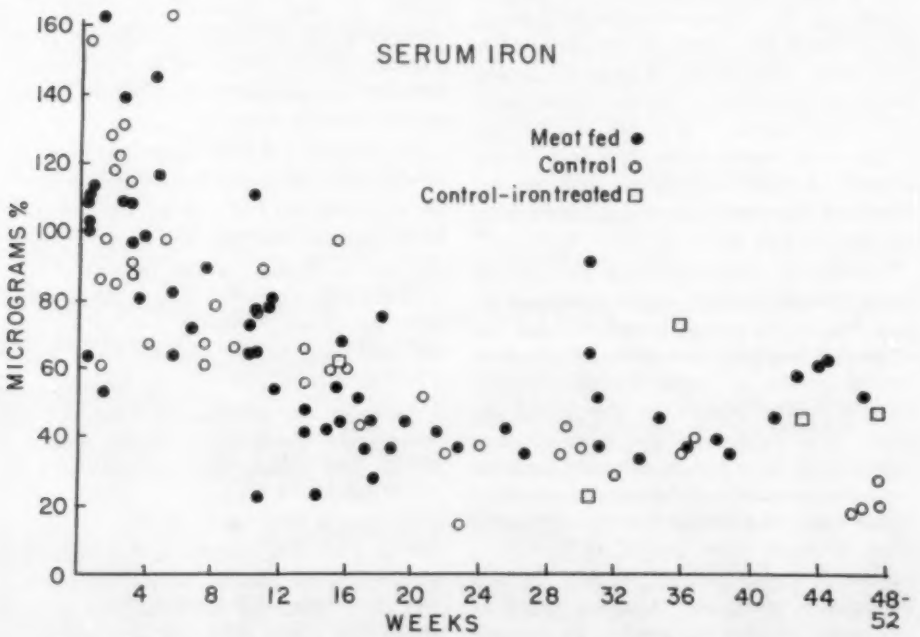


Fig. 4.—The serum iron concentration of both control and meat-fed infants in micrograms per 100 ml. of serum.

The mean serum iron concentration of the meat-fed infants between 30 and 52 weeks was 51μg. per 100 ml., in contrast to the value of 28μg. per 100 ml. found in the control group.

H. Serum Iron-Binding Capacity.—The latent serum iron-binding capacities were absent in slightly more than two-thirds of the infants in the first month of life and gradually increased to 200μg. per 100 ml. by 6 months of age. There was a considerable variation from 200μg. to 500μg. per 100 ml. between 6 and 12 months in both groups.

Comment

Increases in red cell volume and circulating hemoglobin mass occurring between the 6th and 10 the weeks of life in the meat-fed infants were not sustained. However, the time of their occurrence and the generally higher levels maintained in comparison with the control group suggests that the iron source, meat, had an early effect on the synthesis of hemoglobin.

It is true that the amount of meat-iron ingested by the infants was relatively small, but, since it was added to the diet earlier than other solid foods, it provided a distinctly greater amount than was at first available to the controls. It is not claimed that all the iron requirements were met by the amount of meat supplement, but the demands of the rapidly growing infants were satisfied in part.

Increase of marrow activity with growth is not thought to occur in the premature infant before the second month of life,[3] but when that does take place in an infant whose rate of growth is marked the necessity for an iron source other than milk seems obvious. It is suggested that a more adequate reservoir of iron than is naturally available from previous red cell degradation is needed at that time. We believe that the addition of meat in these cases served to provide a portion of such a reservoir of iron for later hemoglobin synthesis. Absolute proof of this would require the tagging of the iron to follow its course in the tissues, marrow, and erythrocytes and to demonstrate the amount absorbed from the intestinal tract.

It is not certain that the quantity of iron derived from degraded red cells in the neonatal period is sufficient for the accelerated synthesis of hemoglobin in the third month of life, when the body weight has at least doubled. Measurement of total circulating hemoglobin mass, though admittedly indirect, exhibited a disappointingly inadequate quantity in the controls after the 12th week. The total amount and the rate of gain were undoubtedly superior in the meat-fed infants. The expansion of red cell volume in these subjects also suggested that a more adequate supply of iron was available when marrow activity increased. It may be that the character of the protein supplement supplied by meat enhanced the expansion of hemoglobin mass and red cell volume.

The steady decline of hemoglobin mass and red cell volume in the control infants demonstrates the need for some effective iron source in the diet of the premature infant. It was apparent that the oral administration of ferrous sulfate and intramuscular administration of ferrous sulfate-dextran were suitable to supply iron for the severely anemic controls.

The distinct and well-maintained increases of red cell volume and hemoglobin mass in the meat-fed infants can be attributed in large measure to the ingestion of meat. Absorption of this iron was perhaps greater than the 10% (approximately) measured in other age groups,[6,7] owing both to the need for iron and to the quantitatively larger iron intake compared with the controls.

Although the addition of meat did not prevent the customary postnatal reduction of red cell volume and hemoglobin mass (and there is no reason it should have), it did assist in a prompt reversal of the fall at least four weeks earlier than this occurred in the control infants. Though not uniformly sustained until the 28th to 30th weeks, the values remained at levels above those recorded in the control group from

the 10th week through the remaining period of study, with few exceptions.

Considered alone, serum iron concentrations are difficult to interpret, since they represent values of iron turnover at the moment of sampling and represent the state of iron stores only indirectly. Coupled with other laboratory determinations they become more expressive of the real condition of iron stores. It was concluded that the values found in the meat-fed group demonstrated that an increase had taken place in those infants after the 28th week.

The most particular benefit from supplementing the diets with meat was the increase of red cell volume, circulating hemoglobin mass, and iron reserves by the end of the first year of life. The amount of meat offered to these infants was limited by considerations of protein intake for the premature infant and not by its digestibility or acceptance. Strained meats were well-tolerated by all the infants, and the frequent gastric distress associated with the administration of medicinal iron was avoided.

Meat provides an excellent protein source for the infant diet and also, we concluded, an acceptable and utilizable source of iron in natural form.

Summary

The addition of meat to the diet of premature infants was studied to assess its influence on red cell volume and circulating hemoglobin mass. Fifteen infants were given strained meats as a dietary supplement from the first month of life, and this addition was continued during the first year. Twenty infants, who served as controls, were denied meat but had otherwise the same diet.

Following the initial decrease in hemoglobin concentration, hemoglobin mass, hematocrit, and red cell volume encountered in all premature infants, there was a temporary increase of these values in the meat-fed subjects between 6 and 8 weeks of age. This did not occur until the 12th week in controls. Steady decline of these values during the first year to low levels was found in the control group, in some instances necessitating medicinal iron therapy. Increases in hemoglobin mass and concentration and hematocrit and red cell volume after after the 30th week were demonstrated in the meat-fed infants.

Serum iron concentrations decreased throughout the period of study in the control subjects. Values for serum iron decreased until the 16th week in the meat-fed group, leveled off until the 30th week, and then increased.

These results suggest that the addition of meat to the diet supplied a pool of iron for subsequent hemoglobin synthesis and that an increase of iron stores had occurred in the infants given this supplement. The expansion of red cell volume and circulating hemoglobin mass in the meat-fed group was greater than in the controls. The steady decline of these values in the control group demonstrates the need for some effective iron source in the diet of the premature infant.

Meat provides an excellent source of protein for the infant diet and, this study indicates, an acceptable and utilizable source of iron in natural form.

Strong Memorial Hospital, 260 Crittenden Blvd. (20).

REFERENCES

1. Merritt, K. K., and Davidson, L. T.: The Blood During the First Year of Life: II. The Anemia of Prematurity, Am. J. Dis. Child. 47: 261, 1934.

2. Tuttle, A. H., and Ettledorf, J. N.: Molybdenized Ferrous Sulphate (Mol-Iron) in the Treatment of the Anemia of Premature Infants, J. Pediat. 41:170, 1952.

3. Schulman, I.; Smith, C. H., and Stern, G.: Studies on the Anemia of Prematurity, A. M. A. Am. J. Dis. Child. 88:567, 1954.

4. Reedy, M. E.; Schwartz, S. O., and Plattner, E. B.: Anemia of the Premature Infant: A 2-Year Study of the Response to Iron Medication, J. Pediat. 41:25, 1952.

5. Sisson, T. R. C.; Emmel, A. F., and Filer, L. J., Jr.: Meat in the Diet of Premature Infants, Pediatrics 7:89, 1951.

6. Smith, N. J.: Personal communication to the authors.

7. Moore, C. V., and Dubach, R.: Observations on the Absorption of Iron from Foods Tagged with Radioiron, Tr. A. Am. Physicians 64:245, 1951.

8. Crosby, W.; Munn, J. L., and Furth, F.: Standardizing a Method for Clinical Hemoglobinometry, U. S. Armed Forces M. J. 5:693, 1954.

9. Nitsche, G. A., and Cohen, P. P.: Simplified Determination of Blood Volume, Am. J. Clin. Path. 17:239, 1947.

10. Allen, T. H.: Extraction of T-1824 in the Presence of Gross Hemolysis and Lipemia, Proc. Soc. Exper. Biol. & Med. 76:145, 1951.

11. Chaplin, H., and Mollison, P. L.: Correction for Plasma Trapped in the Red Cell Column of the Hematocrit Tube, Blood 7:1227, 1952.

12. McGovern, J. J.; Jones, A. R., and Steinberg, A. G.: The Hematocrit of Capillary Blood, New England J. Med. 253:308, 1955.

13. Mollison, P. L.: Blood Transfusion in Clinical Medicine, Ed. 2, Oxford, England, Blackwell Scientific Publications, 1951, p. 91.

14. Burch, H. B.; Lowry, O. H., and Bessey, O. A.: The Determination of Iron in Small Volumes of Blood Serum, J. Biol. Chem. 174:791, 1948.

15. Rath, C. E., and Finch, C. A.: Chemical, Clinical, and Immunological Studies on the Products of Human Plasma Fractionation: XXXVIII. Serum Iron Transport; Measurement of Iron-Binding Capacity of Serum in Man, J. Clin. Invest. 28:79, 1949.

Case Reports

Gynecomastia and Pseudoprecocious Puberty Following Diethylstilbestrol Exposure

MORRIS GREEN, M.D., Indianapolis

The purpose of this paper is to report the occurrence of gynecomastia in a 3-year-old boy and pseudoprecocious puberty in his 23-month-old sister following exposure to diethylstilbestrol (stilbestrol).

Report of Cases

A 3 5/12-year-old white boy was seen in the Yale Private Diagnostic Clinic on Oct. 22, 1956, because of bilateral breast enlargement present since January, 1956. There were no other complaints. Growth and development had otherwise been normal. The child was in the 50th percentile for height and 90th percentile for weight. As illustrated in Figure 1, the breasts were enlarged to a moderate degree. Freely moveable, circumscribed masses of glandular tissue about 2 cm. in diameter were palpable under the areolae. The nipples, areolae, and linea alba were deeply pigmented. A scanty amount of downy pubic hair was present. Axillary hair was absent. Neurologic and funduscopic examinations were negative. The testes were of normal size. No palpable testicular masses were present.

Because of the pigmentation, exposure to exogenous estrogen was considered as an etiologic possibility.[1,2] This suspicion was augmented when it was determined that the father injected diethylstilbestrol paste or implanted diethylstilbestrol pellets into the necks of chickens as a means of "chemical caponization" on his poultry farm. Some of the paste would occasionally spatter on the father's clothes. These were washed along with the rest of the family wash by the mother. Any other exposure of the patient to estrogenic substances was denied. At the conclusion of the visit the mother mentioned that her 23-month-old daughter also had enlarged breasts and asked if she might be seen in the clinic.

Submitted for publication Dec. 23, 1957.

From the Department of Pediatrics, Yale University School of Medicine and the Grace-New Haven Community Hospital. Present address: Indiana University Medical Center. Associate Professor of Pediatrics, Indiana University School of Medicine.

Figure 1

The 23-month-old sister of the boy reported above was first seen on Nov. 3, 1956. History revealed that enlargement of the breasts had been present for four to five months. A whitish vaginal discharge had also been noted from time to time. Physical examination revealed the child to be in the 50th percentile for both height and weight. Breasts were moderately enlarged, as illustrated in Figure 2.

A palpable mass of glandular tissue about 2.5 cm. in diameter was present bilaterally. The nipples, areolae, linea alba, and genitalia were darkly pigmented. A slight amount of downy pubic hair was present. Neurologic and funduscopic examinations were normal. Pigmentation suggestive of the McCune-Albright syndrome was not present. Bimanual examination of the abdomen and pelvis revealed no mass.

At this visit it was learned that the mother had been having two menstrual periods a month, each of six to seven days' duration. The parents also

Figure 2

reported that they had searched the house for diethylstilbestrol pellets and had found a few hundred of them in various drawers. They also recalled having seen the children playing with these pellets but were uncertain as to whether or not any had been ingested. With this additional history, it was decided to delay further diagnostic procedures. The parents were instructed to eliminate the possibility of further diethylstilbestrol exposure. One month later a definite decrease in both breast size and intensity of pigmentation were noted. Vaginal bleeding occurred in the girl two to three weeks after all sources of exogenous estrogenic stimulation had been removed. The mother no longer had two menstrual periods a month. Regression of breast enlargement and pigmentation continued over the next months.

Outside of the neonatal period, gynecomastia is rare in prepubertal boys. Premature development of the breasts is less uncommon in girls. The present report reemphasizes the importance of considering exposure to exogenous estrogenic substances as a cause of gynecomastia or pseudoprecocious puberty. Exposure may be due to inhalation, percutaneous absorption, or ingestion. Intense dark-brown pigmentation of the nipples, areolae, and linea alba are especially suggestive of this etiology.

Hesselvik reported the occurrence of breast development in a 10-month-old boy whose mother had used liberal amounts of diethylstilbestrol ointment for the treatment of eczema of her hands.[3] The hormonal effects in this instance were apparently caused by absorption of the diethylstilbestrol through the infant's skin. Prouty reported the occurrence of gynecomastia in a 4-year-old boy whose mother was employed in the packaging of diethylstilbestrol pellets.[1] The 10-year-old sister of this child also developed breast enlargement, areolar pigmentation, and vaginal bleeding. For a time the mother packaged the pellets by machine at home, and diethylstilbestrol dust was present in the air on a number of occasions. The estrogenic effects here were presumably due to inhalation of the diethylstilbestrol dust and contact with the mother's contaminated clothing. Premature breast development in girls as a result of estrogen ingestion has been described by Cook et al.[2]

It is important to recognize that parents may initially deny the possibility of such exposure. In instances in which exogenous estrogens are thought to account for the findings, observation for a few weeks after cessation of exposure would serve to confirm the diagnostic impression and obviate the need for extensive diagnostic studies. Serial studies of the vaginal epithelium could also be used in girls to demonstrate regression of estrogenic effects.

Summary

The occurrence of gynecomastia in a $3\frac{8}{12}$-year-old boy and of pseudoprecocious puberty in his 23-month-old sister following exposure to diethylstilbestrol is reported. Because of the wide-spread use of estrogenic substances in medicine and in animal husbandry, similar cases may be expected to occur.

Dr. Irwin M. Israel cooperated in the study of these patients.

Indiana University Medical Center, 1100 W. Michigan St. (7).

REFERENCES

1. Prouty, M.: Gynecomastia with Pigmentation in a 4 Year Old Male Following Stilbestrol Exposure, Pediatrics 9:55, 1952.

2. Cook, C. D.; McArthur, J. W., and Berenberg, W.: Pseudoprecocious Puberty in Girls as a Result of Estrogen Ingestion, New England J. Med. 248:671, 1953.

3. Hesselvik, L.: Signs of Sexual Precocity in a Male Infant Due to Estrogenic Ointment, Acta pædiat. 41:177, 1952.

Metaphyseal Dysostosis Resembling Vitamin D-Refractory Rickets

ROBERT EVANS, M.D., and JOHN CAFFEY, M.D., New York

The purpose of this paper is to describe a patient with an unclassified disorder of the metaphyses which, because of clinical, radiographic, and microscopic similarity to vitamin D-refractory rickets, was treated with toxic quantities of vitamin D. The resemblance of the metaphyseal lesions in the present case to the rare condition "metaphyseal dysostosis," described in 1934 by Murk Jansen, is discussed.

Report of Case

The patient, a girl 22 months of age, was admitted to the hospital because of waddling gait and deformity of both lower limbs (Fig. 1).

The child had weighed 3090 gm. at birth. The pregnancy and delivery had been uncomplicated. Growth and mental and motor development had been normal during infancy. A normal diet had been supplemented by percomorph-liver oil (oleum percomorphum), 10 drops each day, since birth. There had been no symptoms suggestive of renal or gastrointestinal disease. The patient appeared to be well until she was noted to have a waddling gait and bow-legged deformity shortly after she began to walk without support, at the age of 16 months. The deformity and gait disturbance had progressed since then, but neither pain nor tenderness of the limbs had been present.

The father had an abnormal curvature of the spine in childhood which had been treated by immobilization in a cast for several months. Subsequent radiographic examination of the extremities and skull of the father during adulthood revealed no skeletal abnormality. Other members of the family are of normal stature, with no history of skeletal disease or deformity. Two brothers, 8 and 10 years, and a sister, 6 years of age, have always been healthy.

Submitted for publication Jan. 2, 1958.

Departments of Pediatrics and Radiology, Columbia University College of Physicians and Surgeons and the Babies Hospital. Trainee, National Cancer Institute (Dr. Evans).

Fig. 1.—Photographs of the patient at the age of 30 months, showing the appearance of the short, bowed lower extremities.

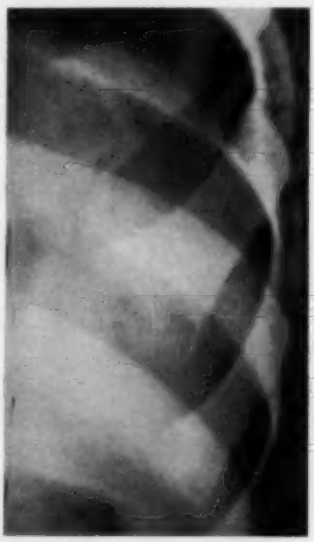
The patient was well developed and well nourished but was short in stature (height, 76 cm.; weight, 11.8 kg.). She stood and walked with an exaggerated lumbar lordosis and had a marked waddling gait. The lower limbs were short in relation to the trunk and arms. The femurs were bowed laterally and anteriorly, and the tibias were bowed laterally. Marked enlargement of the epiphyses at the knees and ankles was visible. Enlargement of the distal epiphyses of the radii and marked notching of the distal tibial and fibular epiphyses were palpable. Muscle volume, strength, and tone were normal. Enlargement at the costochondral junctions of the rachitic type was present, but flaring deformity of the lower thoracic cage or Harrison's groove was not evident. The head was normal, and the anterior fontanel was closed.

Fig. 2.—The pelvis and upper ends of the femurs at the age of 2 years, demonstrating the coxa vara deformities and the irregular radiolucent extensions from the epiphyseal cartilage plates which distort the proximal femoral metaphyses.

The pattern of eruption and the appearance of the 16 teeth were normal.

In the radiographs, the metaphyseal zones of the long tubular bones of the extremities were similar to those of active rickets. All epiphyseal ossification centers were well formed and normally developed. The femoral necks (Fig. 2) were short and broad, and coxa vara deformity was present bilaterally. Abnormally deep radiolucent zones extended irregularly from the epiphyseal cartilages into the proximal femoral metaphyses but were limited at several sites by a narrow peripheral zone of provisional calcification. The radiolucent epiphyseal cartilage plates at the distal femurs and proximal tibias (Fig. 4, *A*) were abnormally deep, and their junctions with the bony metaphyses were irregular in outline, especially in the medial thirds, where long segments of the provisional zones of calcification were irregularly radiolucent. In contrast, the edges of the epiphyseal ossification centers opposite the metaphyses were normal. Tibia vara resulted from angulation at the proximal tibial metaphyses. The distal femoral shafts were bowed laterally. The distal tibial and fibular (Fig. 6, *A*), distal radial and ulnar (Fig. 5, *A*), and proximal humeral metaphyses were affected similarly. A deep irregular radiolucent zone separated the distorted line of provisional calcification at the cup-shaped metaphysis and the normal epiphyseal ossification center. Short projections of radiolucent tissue extended from the epiphyseal cartilage into the diaphyses, but they were smaller than those present at the femoral necks. The shafts of the humeri were broad, short, and equal to the ulnas in length. Flaring of the ventral ends of the ribs (Fig. 3) and irregularity of the contour of the narrow zone of provisional calcification at the costochondral junctions were present. There was no other deformity of the thoracic cage.

Fig. 3.—Flaring of the ventral ends of the left sixth, seventh, and eighth ribs, at the age of 2 years.



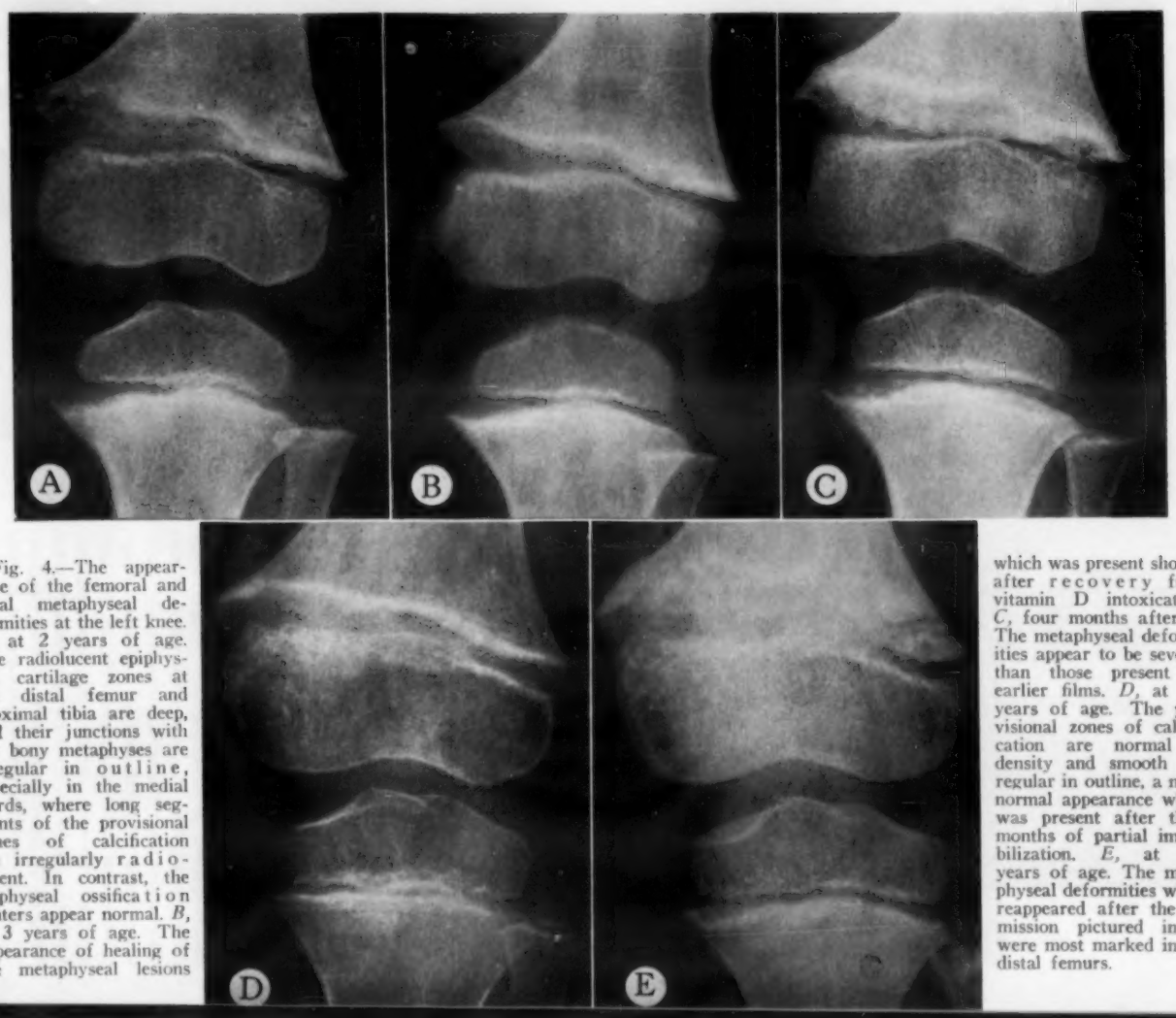


Fig. 4.—The appearance of the femoral and tibial metaphyseal deformities at the left knee. *A*, at 2 years of age. The radiolucent epiphyseal cartilage zones at the distal femur and proximal tibia are deep, and their junctions with the bony metaphyses are irregular in outline, especially in the medial thirds, where long segments of the provisional zones of calcification are irregularly radiolucent. In contrast, the epiphyseal ossification centers appear normal. *B*, at 3 years of age. The appearance of healing of the metaphyseal lesions which was present shortly after recovery from vitamin D intoxication. *C*, four months after *B*. The metaphyseal deformities appear to be severer than those present on earlier films. *D*, at 4½ years of age. The provisional zones of calcification are normal in density and smooth and regular in outline, a more normal appearance which was present after three months of partial immobilization. *E*, at 5½ years of age. The metaphyseal deformities which reappeared after the remission pictured in *D* were most marked in the distal femurs.

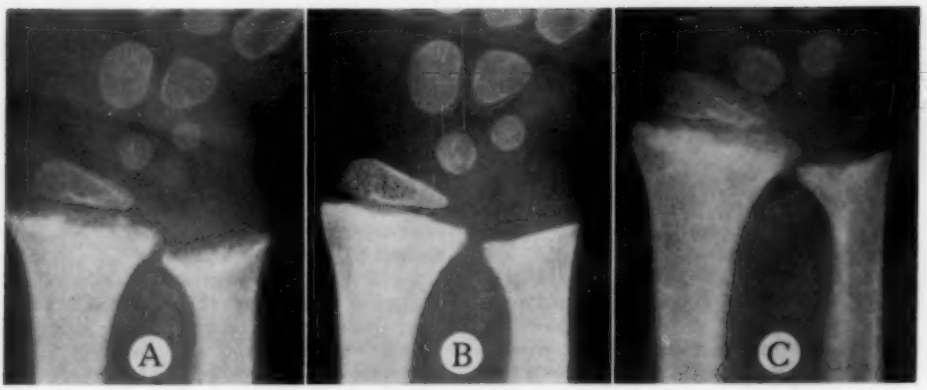


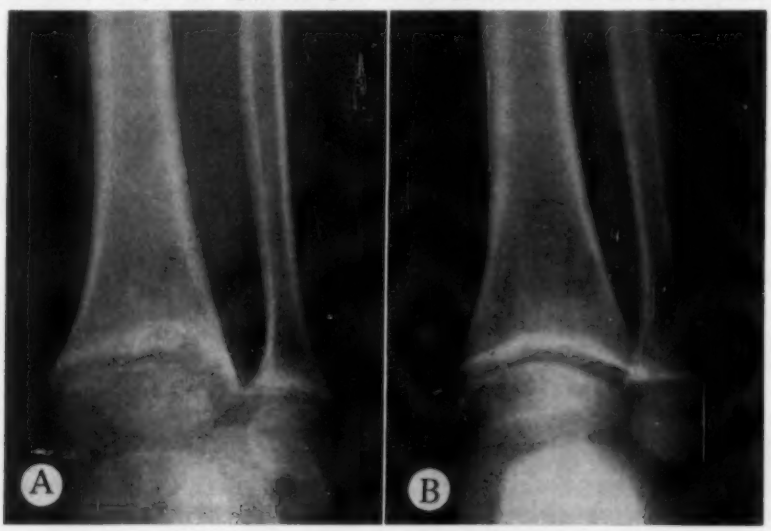
Fig. 5.—Interval changes in the severity of the metaphyseal deformities at the right wrist. *A*, at the age of 2 years. *B*, at the age of 3 years, showing complete healing. *C*, at the age of 4 years; the metaphyseal abnormalities have reappeared.

The radiographic appearance of the skull, teeth, pelvis, spine, scapulae, and clavicles was normal. The radiographic density and the appearance of the cortex and spongiosa of the shafts of the affected tubular bones were normal also. The bones of the hands and feet were not affected. Skeletal maturation, as indicated by the size and number of primary and secondary ossification centers, was normal.

Laboratory data included normal hemoglobin, RBC, and WBC values; normal urinalysis (specific gravity, 1.024; pH, 7.0); negative Mazzini test for syphilis; serum calcium, 11.0 mg. per 100 cc.; serum phosphorus, 4.9 mg. per 100 cc.; serum alkaline phosphatase activity, 8.3 Bodansky units; serum NPN, 36 mg. per 100 cc.; serum CO_2, 17.0 mEq. per liter; serum chloride, 113 mEq. per liter; serum pH, 7.44; normal serum sodium and potassium concentrations. The excretion of phosphate and ammonia nitrogen and the amino acid content of a 24-hour urine specimen were within normal limits. The urinary excretion of calcium was considered to be increased on the basis of a Sulkowitch test result of 3+.

Excision biopsy of the costochondral junction of the right sixth rib was performed. The cartilage

Fig. 6.—The left ankle. *A*, at 2 years of age. The irregularity and deformity of the margins of the distal tibial and fibular metaphyses are similar to those present at the knee and wrist. *B*, at 3 years of age, showing the healed appearance of the metaphyseal lesions.



and bone appeared to be of normal consistency grossly. Upon section, the provisional cartilaginous zone was irregular in outline and varied in width from 1 to 3 mm. At some points, irregular projections of cartilage extended several millimeters into the bony substance. The microscopic section of the rib and costochondral junction revealed abnormalities of the preparatory cartilage zone. The resting cartilage was normal in appearance. The zone of preparatory cartilage was thicker than is usually seen and consisted of columns of 30 to 70 cells. The cells in this zone were not arranged in orderly columns or lacunae but occurred in oval nests and irregular columns. The individual cartilage cells and the cartilage matrix were unremarkable. Large vessels were present between the zones of resting and preparatory cartilage, and smaller vessels were present in an irregular pattern within the preparatory zone. Prolongations of columns and nests of the columnar cartilage zone into the metaphysis produced an irregular and serrated epiphyseal line. A thin zone of provisional calcification was present at the uneven end of the diaphysis. In the zone beyond this, thin bone trabeculae which possessed osteoid tissue at their periphery were seen. The marrow space was filled with normal cellular constituents, and marrow fibrosis was not present. The periosteum and cortical bone were normal. This microscopic appearance of the specimen was reported to be that of rickets.

The findings in this patient were not completely explicable on the basis of vitamin D-refractory rickets or the renal acidosis syndrome associated with renal tubular insufficiency, but, in view of the low serum CO_2 value and the evidence of increased urinary excretion of calcium, a trial of treatment was made with Shohl's citric acid and sodium citrate mixture and 5000 units of vitamin D each day. Two days after this therapy was started the serum CO_2, chloride, and pH values were found to be normal and the Sulkowitch test was 1+. The latter determinations and the values of serum calcium, phosphorus, and alkaline phosphatase activity were normal on several occasions during the following months.

After two months of treatment and enforced reduction of physical activity, marked improvement in the metaphyseal lesions was seen on radiographs. During the summer of her second year the patient's activity was not restricted. Increased physical exercise was followed within two months by a greater degree of abnormality of the metaphyses of the long bones of the extremities. The administration of the citrate and citric acid mixture was discontinued.

The patient was admitted to the hospital again at the age of 30 months because of failure of improvement of the skeletal lesions (Fig. 1). The clinical findings and radiographic appearance of the skeleton were the same as had been noted eight months previously. The serum calcium was 10.4 mg. per 100 cc.; serum phosphorus, 5.3 mg. per 100 cc., and serum alkaline phosphatase activity, 5.5 Bodansky units. The results of the following examinations were normal: urinalysis (specific gravity, 1.025; urine pH, 5.0); urine culture; serum NPN; serum sodium, potassium, CO_2 and chloride concentration; quantitative analysis of a 24-hour urine collection for phosphate, calcium, ammonia nitrogen, titratible acidity, and amino acid content; urinary P. S. P. excretion; urea clearance; renal response to ammonium chloride administration; intravenous pyelogram and cystogram, and slit-lamp examination of the corneas. The serum carotene and vitamin A serum levels, oral glucose-tolerance test, and stool analysis did not provide evidence for malabsorption of vitamin D or calcium.

It was thought then that the metaphyseal lesions were produced by vitamin D-refractory rickets of undetermined cause and that no renal disease was present. The patient was treated with 50,000 units of vitamin D each day and received a regular diet which included 1 qt. of milk each day. After two months, because of lack of improvement of the radiographic abnormalities, the vitamin D dose was increased to 150,000 units each day.

Irritability and anorexia occurred after a four-month period of high vitamin D intake, and the patient was readmitted to the hospital at this time, at the age of 2 years 10 months. Examination showed short stature, accentuated lumbar lordosis, slight enlargement of the costochondral junctions, flaring of the lower rib cage, coxa vara and tibia vara deformities, and palpable enlargement of the epiphyses at the ankles and wrists. The calvarium and teeth appeared normal. Radiographs showed abnormalities at the metaphyses of the long tubular bones which were similar to those in earlier films. The epiphyseal ossification centers, in contrast, appeared normal.

The presence of vitamin D intoxication was established by the presence of episcleral and pericorneal heterotopic calcification. Serum calcium concentration was elevated (15.2-12.2 mg. per 100 cc.), but serum phosphorus and alkaline phosphatase activity were normal. That the elevated serum calcium values were not the result of demineralization of bone was supported by normal calcium balance while on a calcium intake of less than 100 mg. per day. Renal damage due to hypervitaminosis D was evident from serum NPN values of 60 mg. per 100 cc. and an inulin clearance of 14,000 cc. per day (approximately a quarter of the average normal value for children this age). Nephrocalcinosis was not visible radiographically.

The heterotopic calcification disappeared and the serum calcium and NPN values returned to normal within one month after vitamin D was discontinued. During her third year the patient thrived on a regular diet without vitamin D or other medication. Complete healing of the metaphyseal lesions at all sites except the proximal femurs and costochondral junctions was seen on radiographs three months after vitamin D therapy was stopped (Figs. 4, *B*; 5, *B*, and 6, *B*). This change occurred during a period of normal physical activity. The improvement was short-lived, and the metaphyseal deformities returned within four months (Figs. 4*C* and 5*C*).

The coxa vara deformities continued to increase until they were successfully corrected by bilateral subtrochanteric wedge osteotomies during the patient's fourth year. Bony healing at the osteotomy sites was normal and rapid. It is of interest that, after a three-month period of partial immobilization during convalescence from the surgical treatment, radiographic examination of the lower limbs showed definite healing of the metaphyseal lesions at the hips, knees, and ankles; the provisional zones of calcification were normal in density and smooth and regular in outline, and the radiolucent epiphyseal cartilage zones were of normal depth (Fig. 4, *D*). This radiographic improvement was temporary, and the reappearance of metaphyseal lesions at the sites of previous involvement was present three months after the patient had returned to normal physical activity. The deformity of the metaphyses at the distal femurs was more marked than at other sites (Fig. 4, *E*). In spite of these radiographic abnormalities the patient appeared healthy during the three-year period following the orthopedic surgical procedures.

Examination of the patient at the seventh year of age showed a well-nourished girl of small stature (vertex-pubis, 59 cm.; pubis-sole, 46.5 cm.). The palpable enlargements at the costochondral junctions and the epiphyses at the wrists and ankles were less marked. The lumbar lordosis and appearance of the spine were normal. Two normal permanent central incisor teeth had erupted. Radiographs again showed abnormal-appearing radial, ulnar, femoral, tibial, and fibular metaphyses; deep epiphyseal cartilage zones separated the normal epiphyseal ossification centers and the provisional zones of calcification. The latter were of uneven density and irregular and scalloped in margin. Projections of radiolucent tissue extended 1.5 cm. into the metaphyses of the distal femurs and proximal fibulas from the epiphyseal cartilage plates. Some progression of coxa vara deformity had occurred at the right hip in the interval since subtrochanteric osteotomy. The bones of the hands and feet, pelvis, spine, skull, and the shafts of the long tubular bones of the extremities again were well developed, normally formed, and of normal radiographic density.

During the five-year period of observation, the growth and development of the patient's three older siblings and of two younger siblings, born in the interval, have been normal.

Comment

The initial diagnosis of vitamin D-refractory rickets was supported by the clinical, microscopic, and radiographic findings, although the values of serum calcium, phosphorus, and alkaline phosphatase activity were normal. The radiographic abnormalities did not resemble the usual appearance of severe rickets, but the description of the lesions in severe forms of the disease may not fit the mild, chronic example. Chronic rickets, particularly that based on a renal lesion, may exist for years, waxing and waning in severity. Lime salt deposition in portions of the epiphysis-metaphysis junction may continue, and irregular zones of calcification in the cartilaginous matrix may seem particularly dense.[8] During the remission of the metaphyseal lesions in this patient, an irregular line of calcification adjoining the shaft at the periphery of the cartilage projections formed and subsequent calcification occurred contiguous to this and progressed toward the epiphysis. This pattern of healing is unusual in rickets, but it has occurred in exceptional cases.[8]

The pathogenesis of rickets was less easily explained than the appearance of the lesions in the radiographs. Hyperchloremic tubular acidosis was suspected when urine of neutral pH, containing an increased quantity of calcium, was produced in the presence of hyperchloremia and a low serum CO_2-combining power. The normal serum chemical values and normal renal function found later did not support the diagnosis of vitamin D-refractory rickets caused by renal tubular dysfunction. There was no evidence of malabsorption of vitamin D or of calcium.

The healed appearance of the metaphyseal lesions which was seen several months after treatment with high doses of vitamin D

may not be due solely to the effects of the vitamin, in view of the remissions and relapses that occurred prior to and subsequent to that therapy. There seems to be a better causal correlation between reduced physical activity of the patient and improvement of the metaphyseal abnormalities.

Many patients with vitamin D-refractory rickets tolerate large doses of vitamin D over long periods, but this patient developed signs of toxicity due to hypervitaminosis D after a four-month period of relatively small daily doses. Hypercalcemia, heterotopic tissue calcification, and renal damage developed. Calcification in the kidneys is of paramount importance and is the greatest danger of incorrect diagnosis in patients whose disease simulates vitamin D-refractory rickets. The glomerular and tubular damage produced thus leads to progressive impairment of renal function and renal failure if the toxic doses of vitamin D are not discontinued.

Administration of large doses of vitamin D has been found to be a precarious form of treatment in another disease resembling rickets clinically, radiographically, and microscopically—hypophosphatasia.[4] The latter is a rare inherited disorder of bone mineralization characterized by diminished alkaline phosphatase activity in serum and tissues. In radiographs, the metaphyseal lesions in older children with hypophosphatasia resemble those in the present case, but cyclic remission and relapse has not been reported in the former. Several groups have administered large doses of vitamin D to these patients on the basis of the features which resemble rickets. Toxicity due to hypervitaminosis D occurred rapidly on numerous occasions,[4] and the beneficial effects of this therapy have been unconvincing.

After doubt of the diagnosis of rickets increased, the rib biopsy specimen was restudied by several pathologists. It was the consensus that the abnormal cartilage growth and endochondral bone formation could be explained as an atypical chondrodystrophy or dyschondroplasia rather than as rickets. The quantity of osteoid tissue was not abnormal. The report of broad osteoid zones surrounding the bone trabeculae at the initial examination may have been based on an artifact produced by prolonged decalcification.

The disturbance of cartilaginous growth and endochondral bone formation in this patient resembles superficially that in achondroplasia and dyschondroplasia. The distribution of lesions in the long tubular bones, the relative enlargement of the epiphyseal cartilages, and the irregularity of the zones of provisional calcification produced by unequal growth of the cartilage in different segments of the metaphyses; the involvement of bones in proportion of the magnitude of their endochondral growth; the presence of normal ossification centers in the epiphyses, and shortening of the affected bones—all may be features in common. But in achondroplasia the absence of a columnar zone of cartilage cells and a paucity of proliferating cartilage cells are characteristic,[1] and the vertebral bodies, sacrum, scapulae, sternum, and cartilaginous base of the skull are often hypoplastic. In the typical example of dyschondroplasia, cartilage masses are distributed irregularly and often occur as isolated enchondromata in the shafts of tubular bones, ilia, and scapulae. The difference in microscopic appearance of the affected growing ends of bones in this patient and that reported in dyschondroplasia[10] may be one of degree. There is a wide variation in the magnitude of the abnormalities in different patients with achondroplasia and dyschondroplasia, and the criteria for diagnosis of the mild case are not precisely defined. Remissions and relapses of the radiographic abnormalities, important features of the present case, are not the expected course of either dyschondroplasia or achondroplasia.

In a discussion of congenital bone dystrophies, Sear[9] mentions a boy 9 years of age with a symmetrical and generalized cartilaginous dystrophy affecting only the

metaphyses of tubular bones. Irregular projections into the ends of the shafts from the epiphyseal cartilage plates produced distorted zones of provisional calcification, but no isolated enchondromata were found. Sear considered his case to be either a variant of Ollier's disease or an example of a condition which he considered to be closely related to Ollier's disease, "metaphyseal dysostosis."

In 1934 Murk Jansen [5] described an unusual case of disturbance of endochondral bone growth which he labeled "metaphyseal dysostosis," and to which Sear referred. The patient was a dwarfed boy with short and deformed lower limbs. There was a severe generalized deformity of the metaphyses, and there were deep lucent zones between the latter and the normal-appearing epiphyseal ossification centers. The margin of the acetabulum, the posterior aspect of the calcaneus, and the short tubular bones of the hand were affected, as well as the large bones of the extremities. Microscopic examination of a fragment from the lower end of the tibia showed cartilage cells of irregular size and arrangement, with a distorted zone of provisional calcification and isolated masses of bone within the substance of the cartilage. An incomplete description of the clinical and laboratory features in Jansen's case prevents careful comparison with examples of so-called metaphyseal dysostosis reported later.

Details of Jansen's single case were described by Fairbank,[3] who mentioned briefly two similar patients who had been brought to his notice. A report of one of these patients was later published by Müller and Sissons.[7] They stated that the radiographic changes and microscopic skeletal abnormalities found at necropsy, although showing some similarity to those in Jansen's patient, were consistent with a diagnosis of renal osteodystrophy and secondary hyperparathyroidism.

In 1954 Cameron et al.[2] reported on skeletal lesions in a dwarfed Chinese boy 7 years of age which fit the descriptive title of metaphyseal dysostosis. Marked disturbance of endochondral bone growth was present at sites where such growth is normally most active and was limited to the metaphyseal side of the epiphyseal cartilage. In addition to the long bones of the extremities, the costochondral junctions, margins of the acetabula and glenoid fossas, crests of the ilia, inner ends of the clavicles, tubular bones of the hands and feet, sacroiliac and ischiopubic synchondroses, and the base of the skull were affected. The serum calcium, phosphorus, and alkaline phosphatase activity were normal. The main abnormality in a biopsy specimen from the distal portion of the femur consisted of the presence of irregular masses of abnormal cartilage in the metaphyseal region. No change in the severity of the deformities occurred during a two-year period of observation.

Lenk [6] recently discussed the radiographic appearance of the skeleton of a girl, 2 years of age, who had generalized metaphyseal deformities which he called metaphyseal dysostosis. The description of Lenk's patient and the distribution and appearance of the metaphyseal lesions in radiographs are practically identical to those found in the present case. His patient, too, had been thought to have rickets and had received vitamin D without improvement. Laboratory data, biopsy, and the clinical course of the patient are not described in Lenk's article.

Some authors have regarded metaphyseal dysostosis as a distinct cartilaginous dystrophy, and others have implied that it is an atypical example of either achondroplasia or dyschondroplasia. The case reports are too few and incomplete to be a basis for either conclusion, and it is apparent that little factual information is available. The term "metaphyseal dysostosis" would seem to be a useful label by which similar cases might be indexed for review at a time when more is known of their pathogenesis and natural course. For the present, it is important that physicians be aware of a disease which may resemble vitamin D-refractory

rickets clinically and radiographically, in order that they may avoid the administration of toxic quantities of vitamin D to such patients.

622 W. 168th St. (32).

REFERENCES

1. Caffey, J.: Achondroplasia, in Brennemann's Practice of Pediatrics, Hagerstown, Md., W. F. Prior Co., Inc., 1957, Vol. 4, pp. 1-22.

2. Cameron, J. A. P.; Young, W. B., and Sissons, H. A.: Metaphysial Dysostosis, J. Bone & Joint Surg. 36-B:622-629, 1954.

3. Fairbank, T.: An Atlas of General Affections of the Skeleton, Baltimore, Williams & Wilkins Company, 1951, pp. 85-88.

4. Fraser, D.: Hypophosphatasia, Am. J. Med. 22:730-746, 1957.

5. Jansen, M.: Über atypische Chondrodystrophie (Achondroplasia) und über eine noch nicht beschriebene angeborene Wachstumsstörung des Knochensystems: Metaphysäre Dysostosis, Ztschr. orthop. Chir. 61:253-286, 1934.

6. Lenk, R.: Hereditary Metaphyseal Dysostosis, Am. J. Roentgenol. 76:569-575, 1956.

7. Müller, G. M., and Sissons, H. A.: A Case of Renal Rickets Simulating "Metaphysial Dysostosis," J. Bone & Joint Surg. 33-B:231, 1951.

8. Park, E. A.: Observations on the Pathology of Rickets with Particular Reference to the Changes at the Cartilage-Shaft Junctions of the Growing Bones, Harvey Lect. 34:157-213, 1938-1939.

9. Sear, H. R.: The Congenital Bone Dystrophies and Their Co-Relation, J. Fac. Radiologists 4:221-234, 1953.

10. Speiser, F.: Ein Fall von systematisierter Enchondromatose des Skeletts, Arch. path. Anat. 258:126-160, 1925.

Coexistent Pregnancy of Unequal Twins

HENRY K. SILVER, M.D., Denver, and PETER CUNNINGHAM, M.D., New Haven, Conn.

Multiple births occur approximately once in every 87 pregnancies, and in almost all instances that result in live births the infants are approximately of the same degree of maturity and have relatively similar weights. Occasionally however, there is a marked difference in the size, weight, and apparent maturity of the infants. The purpose of this paper is to report a set of live-born dizygotic twins weighing 2 lb. 8 oz. (1130 gm.) and 6 lb. (2710 gm.), respectively, with a marked dissimilarity in size and maturity and to discuss the possible mechanisms involved in producing the variations noted.

Case History

Male twins were born at full term of a 33-year-old woman after a pregnancy which had been complicated by a nephrectomy during the second month of pregnancy because of hematuria, "staghorn calculus," and pyelonephritis. The first twin weighed 6 lb. (2710 gm.); the second, 2 lb. 8 oz. (1130 gm.). The placenta measured 21×27 cm. and weighed 1 lb. 7 oz. (635 gm.). It was obscurely divided into two parts, one measuring about 21×18 cm.; the other, about 13×9 cm. There were two sets of membranes, with the smaller set giving the appearance of having invaginated the larger so that the reconstructed dome of the smaller bag appeared to be within that of the larger. No unusual infarcts were seen in either of the two placentas. A normal-sized umbilical cord came from the larger portion of the placenta to the larger of the twins; a smaller twisted one came from the smaller placenta. No histological examination was made of the placenta or membranes.

The first twin breathed spontaneously and seemed normal in all respects. He was 47.0 cm. long, with a head circumference of 34 cm. and a chest circumference of 30 cm. A moderate amount of breast tissue could be palpated. He had an uneventful hospital course and was discharged with his mother at 5 days of age. The smaller twin needed resuscitation. He was 37 cm. long, with a head circumference of 29.8 cm. and a chest circumference of 23 cm. He had the appearance of the usual very small premature infant. No breast tissue could be palpated. A first degree hypospadias was present. He began to have convulsions at the age of 6 hours, and these continued intermittently until his death, at the age of 28 hours. Postmortem examination was not performed.

Roentgenograms for determining skeletal maturation (Figure) showed that the first and larger twin had well-visualized centers of ossification in the epiphysis at the distal end of the femur and proximal end of the tibia, while the second twin had only beginning ossification of the distal femoral epiphysis and absence of ossification in the epiphysis at the proximal end of the tibia. These were interpreted as showing that the larger twin had a "bone age" which was average for the usual full-term boy while the second twin had a "bone age" comparable to that usually seen in male infants about four to six weeks before term.

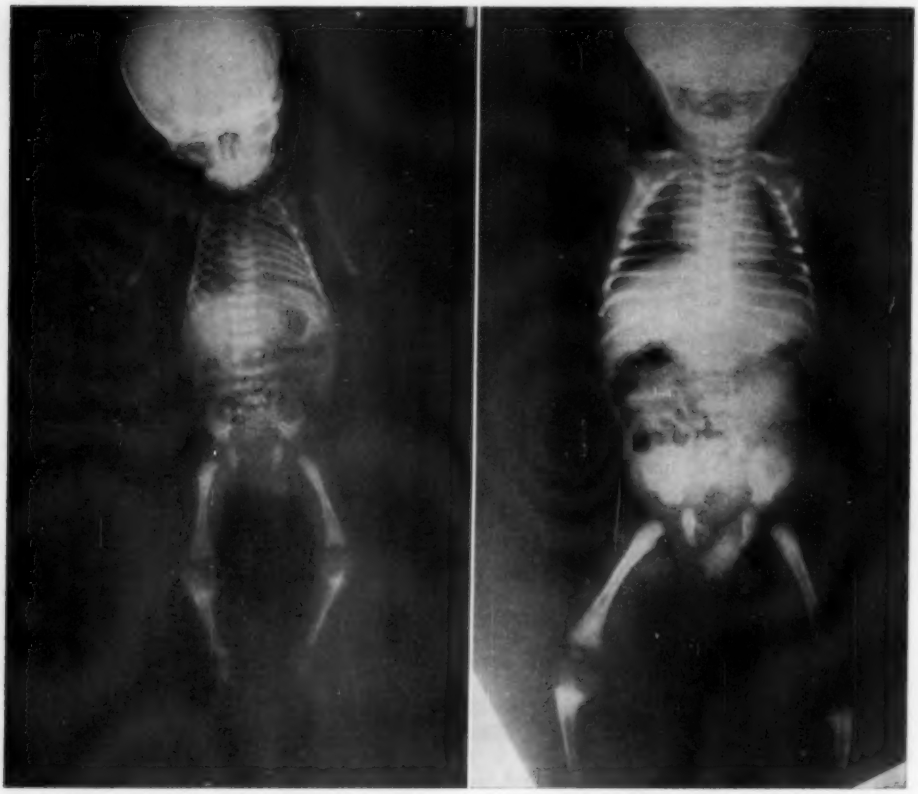
Comment

These male twins, born of a mother who had a nephrectomy during the second month of pregnancy, showed a marked difference in weight, size, and apparent maturity. The smaller of the twins had all of the characteristics attributed to the premature infant, while the larger appeared to have the development usually seen in the healthy full-term infant (Table). Although there are no absolute or definite standards to differentiate the premature and full-term infant, various criteria are used to determine whether or not a particular child was born prematurely.[1] The presence of most of these criteria in any particular infant usually indicates prematurity, while their absence makes this diagnosis much less likely.

Received for publication Jan. 9, 1958.

Dr. Gerald Krosnick, Department of Obstetrics, Yale University School of Medicine, assisted in this study.

From the Departments of Pediatrics, University of Colorado School of Medicine (Dr. Silver) and Yale University School of Medicine (Dr. Cunningham).



Photograph of roentgenograms of twins taken during first day of life. Note the difference in skeletal size and epiphyseal maturation.

Various explanations have been presented to account for the marked differences in development and size that are sometimes present in twin births. It has been postulated that they occur because of a difference in intrauterine nutrition, with resultant retardation in the development of the poorly nourished one. Another explanation for the disparity is that fertilization and implantation of a second ovum liberated by an independent ovulation occured at some time after the first fertilized ovum became established in the uterus. This process is called superfetation. Many instances of suspected superfetation have been reported in humans, including those of Ahlfeld,[2] who reported cases in which living twins weighed, respectively, 5 lb. 1 oz. (2320 gm.) and 2 lb. 8 oz. (1120 gm.) and 4 lb. 4 oz. (1920 gm.) and 1 lb. 12 oz. (790 gm.), and Gustetter,[3] who reported two fetuses in which the difference in the apparent ages of the two was felt to be as great as 65

Comparison of the Physical Development and Maturity of the Twins

Criteria of Prematurity *	First Twin	Second Twin
Birth weight less than 5½ lb. (2,500 gm.)	No (2,710 gm.)	Yes (1,130 gm.)
Crown-heel length less than 47 cm.	No (47 cm.)	Yes (37 cm.)
Head circumference less than 33 cm.	No (34 cm.)	Yes (29.8 cm.)
Chest circumference less than 30 cm.	No (30 cm.)	Yes (23 cm.)
Chest circumference / Head circumference = less than 92%	Yes (89%)	Yes (77%)
Difference between head and chest measurement more than 3 cm.	Yes (4 cm.)	Yes (6.8 cm.)
Absence of ossification center for proximal tibial epiphysis	No	Yes
Absence of palpable breast tissue	No	Yes
General appearance of prematurity	No	Yes

* Adapted from Dunham.[1]

days. Sussi [4] described the delivery of a living boy weighing 6 lb. 14 oz. (3110 gm.) and measuring 48 cm. who had as a co-twin at the same birth a living girl weighing 15 oz. (420 gm.) and measuring 28 cm. Schaab [5] studied binovular twins weighing 4 lb. 2 oz. (1900 gm.) and 6 lb. 4 oz. (2850 gm.) at birth in whom roentgenographic studies showed marked differences in epiphyseal maturation. He concluded that their development differed by at least a month. In his very comprehensive review of the literature, Studdiford [6] reports other cases in which two or more fetuses were passed who had a marked difference in size and appearance.* He also describes instances, especially in the older literature, of pregnancies which went to term with the delivery of two or more fetuses with a marked variation in size. These included patients who delivered a term infant and followed this after an interval of one to three months by delivering a second infant also at term. In regard to these cases, Studdiford felt that they were "almost unbelievable," and he could find no such instance in the more recent literature. He concluded that none of the cases in the literature proved the process of superfetation in the human, although a few reported cases suggested that such an occurrence was possible.

Although many investigators believe that superfetation is possible in animals [8,9] in whom oestrus and ovulation during pregnancy has been shown to take place, others [10] are of the opinion that a second pregnancy in animals probably never occurs and that cases of superfetation may be explained by variations in the time of implantation among the same set of fertilized eggs.

In considering the theoretical possibility that superfetation might occur, it would be necessary for ovulation, fertilization, and nidation to take place after a pregnancy has been established in the uterus for at least a month. This is extremely unlikely in the human, since the action of pituitary hormones tends to suppress ovulation during pregnancy.[11] Even though maturation of a second ovum may occasionally take place during human pregnancy, this almost invariably terminates in degenerative changes and atresia.[6] In any case, superfetation would be out of the question after the third month of pregnancy, when the fusion of the decidua vera and reflexa occurs. Where one or both of the twins are born dead, marked variations could be the result of the retention of the dead twin in the uterus for an appreciable time before delivery, during which it might only show minimal changes in form or gross structure.

Superfetation, if it does occur, is most likely to take place in a double uterus, but Salfelder and Lambertz [12] have pointed out that the proof of superfetation in man can only be made when the twin births have resulted from fertilization of two ova at different times and during different ovulation periods by fathers who are of different races. Of course, such an occurrence is very unlikely to take place.

Although there was a marked dissimilarity in the size and development of the twins herein reported, it is our impression that the diversity could be explained by a probable difference in nutrition of the two fetuses as a result of the variations noted in the placentas rather than by the phenomenon of superfetation.

Summary

A coexistent pregnancy of unequal live-born twins weighing 6 lb. (2710 gm.) and 2 lb. 8 oz. (1130 gm.), respectively, with marked differences in size and maturity, is presented.

The mechanisms that might produce this condition are discussed.

4200 E. 9th Ave. (20).

* In this regard it is of interest to note that Potter and Fuller [7] have reported on a large series of twin births seen at the Chicago Lying-In Hospital. They found that the average difference in weight between the first and second twin was roughly 400 to 500 gm. in those born between the 265th and 295th days.

REFERENCES

1. Dunham, E. C.: Premature Infants: A Manual for Physicians, New York, Paul B. Hoeber, Inc. (medical book department of Harper & Brothers), 1955.

2. Ahlfeld, F.: Beiträge zur Lehre von den Zwillingen, Arch. Gynäk. 9:196, 1876; quoted by Eastman, N. J., in Williams Obstetrics, Ed. 11, New York, Appleton-Century-Crofts, Inc., 1956, p. 662.

3. Gustetter, A. L.: Abortion Due to Superfetation, J. A. M. A. 70:20, 1918.

4. Sussi, L.: Ein Fall von Superfaetatio, Med. Klin. 31:1334, 1935.

5. Schaab, A., quoted by Studdiford.[6]

6. Studdiford, W. E.: Is Superfetation Possible in the Human Being? Am. J. Obst. & Gynec. 31: 845, 1936.

7. Potter, E. L., and Fuller, H.: Multiple Pregnancies at the Chicago Lying-In Hospital, 1941 to 1947, Am. J. Obst. & Gynec. 58:139, 1949.

8. Wislocki, G. B., and Snyder, F. F.: Experimental Acceleration of Rate of Transport of Ova Through Fallopian Tube, Bull. Johns Hopkins Hosp. 52:379, 1933.

9. Fleming, G.: Veterinary Obstetrics, London, Baillière, Tindall & Cox, 1930, p. 127.

10. Weichert, C. K.: A Case of Parallel Embryonic Development in the Rat and Its Bearing on the Question of Superfetation, Anat. Rec. 83: 511, 1942.

11. Rollhäuser, H.: Superfetation in a Mouse, Anat. Rec. 105:657, 1944.

12. Salfelder, K., and Lambertz, H. J.: Zur Frage der Superfetation und der Abortiveier bei Mehrlingsschwangerschaften: Bericht über Mehrlingsschwangerschaften: Bericht über einen Fall und Literaturübersicht, Geburtsh. u. Frauenh. 11: 50, 1951.

Progress in Pediatrics

The de Toni-Fanconi Syndrome with Cystinosis

Clinical and Metabolic Study of Two Cases in a Family and a Critical Review on the Nature of the Syndrome

HOWARD G. WORTHEN, M.D., and ROBERT A. GOOD, Ph.D., M.D., Minneapolis

The de Toni-Fanconi syndrome * is a clinical constellation characterized by resistant rickets, acidosis, glycosuria, hyperamino-aciduria, and organic aciduria. This syndrome belongs to a group of diseases based on abnormalities in renal tubular function. The renal abnormality in patients with the Fanconi syndrome consists of a deficient tubular reabsorption of phosphorus, amino acids and glucose along with a deficiency in the tubular mechanism for reabsorbing base without acid. In a number of children having clinical evidence of the Fanconi syndrome, postmortem histological studies have revealed deposits of cystine crystals scattered throughout various organs and tissues of the body, particularly in the reticuloendothelial system. In recent years an increasing number of instances have been reported in which cystinosis has been detected ante mortem by examination of bone marrow aspirates or by a slit-lamp examination of the cornea of the eye. In Table 1 are tabulated a number of cases [1-53] which have appeared in the literature since McCune et al.[36] published the cases reported up to 1941. It will be noted that the frequency of antemortem diagnosis of cystinosis is increasing. The frequency of this association has led many investigators to the conclusion that cystinosis and the Fanconi syndrome represent a single disease entity based on a metabolic disturbance involving the sulfur-containing amino acids or on a generalized disturbance of protein metabolism producing both cystinosis and the renal abnormalities. However, in other typical cases of the Fanconi syndrome autopsy examination has not revealed cystinosis, which implies that the two conditions are not necessarily mutually inclusive. At the present time we must conclude that the etiology and pathogenesis of this clinical syndrome as it occurs naturally remain obscure. Indeed, it seems quite possible that several entirely different metabolic disturbances might lead to the type of tubular malfunction that results in the clinical manifestations recognized as the Fanconi syndrome.

Much research has been directed toward the elucidation of the pathologic physiology responsible for the tubular dysfunction in this syndrome.[2,7,22,31,43] As a result of these studies, a more rational approach to therapy has resulted in clinical improvement in a number of cases.[22,31,42] But even in cases where the acidosis and rickets have been brought under control by the use of adequate base and vitamin D therapy, progres-

Submitted for publication Nov. 19, 1957.

Aided by grants from the Hill Family Foundation, American Heart Association, Minnesota Heart Association, and the U. S. Public Health Service (E-798 and H-2085).

From the Department of Pediatrics and the Pediatric Research Laboratories of the Variety Club Heart Hospital, University of Minnesota Medical School. American Legion Memorial Heart Research Professor of Pediatrics (Dr. Good).

* Generally referred to in the European literature as the de Toni-Debre-Fanconi syndrome, after the three initial investigators. For the sake of brevity, we shall term it merely the Fanconi syndrome, since it will be understood that it is Fanconi's rachitic syndrome which is intended.

TABLE 1.—*Summary of Cases in the Literature Since 1941*

Author	Sex	Age	Consanguinity	Fanconi Syndrome	Cystinosis	Comment
Fanconi [1]						
Case 2	F	Early	No	Complete [*]	--	Died at 5 yr.; no autopsy
Case 3	F	Early	No	Complete	Yes	Autopsy: cystinosis; kidney damage, glomerular and tubular
Stowers & Dent [2]	M	47	No	Complete	No	Autopsy: no cystinosis, no phosphatase in proximal tubules, nodular cirrhosis & hepatoma
Hottinger [3]	F	10 mo.	No	Rickets but no glycosuria	Yes	Autopsy: normal kidneys
Maschas et al. [4]	M	Alive at 18 yr.	Yes	Rickets, but no glycosuria or acidosis	Yes	Severe cystinuria with frequent stone formation
Ullrich [5]	M	Alive at 12	Yes	Unknown; renal failure when first seen	Yes, cornea	6 siblings died with similar symptoms
D'Avignon & Vahlquist [6]	M	14 mo.	No	Complete	Yes, cornea	
Linder et al. [7]	F	13	No	Complete	No	Patient has retinitis pigmentosa, & a sister has similar symptoms and retinitis pigmentosa
Fanconi & Bickel [8]						
Case 1	M	2.5 yr.	Yes	Complete	No	Glycogen-storage disease
Case 2	F	18 mo.	No	Complete	Yes	Brother died at 3 yr. of cystinosis
Hingston [9]	F	11 mo.	No	Complete	?	Father died of a renal calculus; brother died of a renal disease accompanied by glycosuria
Melle & Barnes [10]	M	Onset at 2 yr.	No	Complete	No	No cystine found in bone marrow; patient still alive
Barnes [11]	F	2 yr.	No	Complete	No	No cystine in marrow; patient still alive
Bakx [12]	F	4 yr.	No	Complete	Yes, cornea	
Douglas [13]	F	6 yr.	--	Complete	Yes, cornea	
Stevenson [14]	M	15 mo.	--	Complete, except no acidosis	No	Urine became normal after rickets were healed with vitamin D
Dent & Harris [15]						
Case 1	F	41	No	Complete	No	Healed with alkali, calcium, & vitamin D
Case 2	M	43	No	No symptoms; glycosuria	No	Asymptomatic siblings of Case 1
Case 3	F	41	No	and albuminuria present	No	discovered on routine testing;
Case 4	M	37	No	No bone changes, but chemical osteomalacia present in all	No	all had typical amino-aciduria
Case 5	M	10	No	Complete	No	No cystine crystals in cornea; rickets completely healed by vitamin D
King & Lockridge [16]	M	Early; died at 3 yr.	No	No rickets; otherwise typical	Yes	Autopsy: cystinosis; degeneration of proximal tubules, normal glomeruli; no ricktes
Monod [17]	M	22 mo.	No	Complete, except that CO_2 was normal	Yes, cornea & bone marrow	Sister also had cystinosis
Linneweh [18]	M	Onset at 1 yr.; seen at 7 yr.	Yes	Complete	Yes, cornea & bone marrow	2 sisters died of cystinosis; autopsy: cystinosis, atrophic kidneys
Drablos [19]	F	2 yr.	No	Complete, except for only slight acidosis	Yes, cornea	Autopsy: cystinosis; normal kidneys
Muller [20]	M	9 yr.	--	Complete	Yes, cornea	
Braendstrup [21]						
Case 1	F	21 mo.	No	Complete	Yes, cornea	"Electrolyte death"; kidneys normal at autopsy
Case 2	F	18 mo.	No	Complete; progressive renal insufficiency	Yes, cornea	
Bickel et al. [22]	M	6 mo.	No	All complete, with typical	Yes →	Amino-aciduria & glycosuria disappeared after the rickets and acidosis were corrected
	F	9 mo.	No	symptoms, physical findings, & chemical changes; cystinosis found in all by slit-lamp examination of cornea and/or bone marrow aspiration	Yes	
	M	9 mo.	No		Yes	
	F	6 mo.	No		Yes	
	M	14 mo.	No		Yes	Rickets healed with vitamin D
	M	6 mo.	No		Yes	Died at 3 yr., cystinosis
	M	15 mo.			Yes	Died at 2 yr., normal kidneys
	F	18 mo.	No		Yes	Died at 10 yr., scarred kidneys
Philpott et al. [23]	M	3 yr.	No	Complete	Yes	Decreased amino-aciduria and glycosuria after alkali and vitamin D
	M	2 yr.	No	Complete; gradual renal failure	Yes	
Guild et al. [24]	M	19 mo.	No	Complete; progressed to renal failure	Yes, cornea	
	F	--	No	Complete; progressed to renal failure	Yes, cornea	

TABLE 1.—*Summary of Cases in the Literature Since 1941*—Continued

Author	Sex	Age	Consanguinity	Fanconi Syndrome	Cystinosis	Comment
Kennedy [24]	M	17 mo.	..	Complete	Yes, cornea	
	M	3 yr.	..	Polyuria, polydipsia, & albuminuria; no other findings reported	Yes, cornea	
Brown [25]	F	7 mo.	Yes	Unknown; blind from birth, slow growth, constipation, vomiting; died with dehydration of sudden onset	Yes, autopsy	Autopsy: tubular atrophy, dilated cortical tubules, lined with low cuboidal epithelium
	M	15 mo.	Yes	Complete; progressive renal failure	Yes, autopsy	Sibling of Case 1; autopsy showed fibrotic kidneys, with calcification of tubules & glomeruli
Weyers [27]	F	1 yr.	Yes	Complete; progressive renal failure	Yes, cornea & marrow	
Williamson [28]	F	3 yr.	..	Probably early onset; renal failure by 5 yr.; tetany, hyperchloremia; & hypokalemia	Yes, cornea	Choroidoretinal degeneration, with partial optic atrophy; autopsy: gross kidney damage
Boehncke et al. [29]	..	11 mo.	Yes	Complete	Yes, cornea & marrow	
Harper et al. [30]	F	5 mo.	No	Complete; very early onset with progressive renal failure	Yes, autopsy	Autopsy: hyperparathyroidism abnormalities of proximal tubule
	F	2 yr.	No	Complete	Not found	
Milne et al. [31]	F	51 yr.	No	Complete	No	Excessive urinary bicarbonate with decreased ammonia and titratable acid
Anderson et al. [32]	F	44 yr.	No	Complete	No	
Dimson [33]	M	1 yr.	No	Complete	Yes, cornea	Moderate improvement with vitamin D and sodium citrate; corneal cystine decreased by α-tocopherol
	F	2 yr.	..	Complete	Yes, cornea	
Jackson & Clark [34]						
Case 1	M	6 mo.	..	Glycosuria and aminoaciduria not reported; otherwise complete	Yes	Autopsy: cystinosis
Case 2	F	6 mo.	..	Same	Yes	Autopsy: cystinosis
Weber [35]	M	1 yr.	No	No; no glycosuria, no amino-aciduria; hyperchloremic acidosis was present, with decreased ammonia & titratable acidity	Yes	Seen after serum phosphorus was elevated; no possibly glomerular function was depressed enough to prevent amino-aciduria and glycosuria
Freudenberg [36]	F	9 mo.	..	Complete	Yes, cornea & bone marrow	Tyrosine in marrow & urine
Caussade et al. [37]	M	8 mo.	..	No; no glycosuria or acidosis; NPN, 63 mg.	Yes, cornea & marrow	
Kyle et al. [38]	M	51 yr.	No	Complete	No	
Myerson & Pastor [39]	M	56 yr.	No	Complete	No	Carcinoma of pancreas
Burki [40]	F	6 mo.	..	Complete	Yes, cornea	
Bickel & Thursby-Pelham [41]	M	15 mo.	No	Complete	Yes, cornea & marrow	Amino-aciduria & glycosuria disappeared & rickets healed after treatment with vitamin D & alkali
	..	5 mo.	No	Complete	Yes, cornea & marrow	
Salassa et al. [42]	M	7 yr.	No	Complete	Not mentioned	Decreased amino-aciduria & glycosuria after massive vitamin D therapy
	F	8 yr.	No	Complete		
Sirota & Hamerman [43]	M	54 yr.	No	Complete	No	Developed multiple myeloma
Perry et al. [44]						
Case 1	F	8 mo.	No	Complete	Yes	Early renal failure
Case 2	M	18 mo.	No	Complete	Yes	
Israels & Suderman [45]	M	9 mo.	No	Complete	Yes, cornea	
Lathem et al. [46]	F	Onset ?; 3 yr. when reported	..	Complete	Unknown (not mentioned)	
Schiff [47]	M	2½ yr.	..	Complete	Yes, cornea	
Gatzimos et al. [48]	F	6 mo.	..	Complete	Yes, autopsy	
Parker et al. [49]						
Case 1	M	6 mo.	No	Complete	Yes, bone marrow	Normal kidneys & parathyroids at autopsy
Case 2	M	8 mo.	No	Complete	Yes	Amino-aciduria & glycosuria reduced by vitamin D

TABLE 1.—*Summary of Cases in the Literature Since 1941*—Continued

Author	Sex	Age	Consanguinity	Fanconi Syndrome	Cystinosis	Comment
Cogan et al.[10]						
Case 1	M	2 yr.	..	Complete, late case; NPN, 91 mg.	Yes, cornea	
Case 2	M	2 yr.	..	Partial; also neph. diab. insip.	Yes, cornea	
Case 3	M	2 yr.	..	Unknown; not complete	Yes, cornea & kidney, biopsy	
Case 4	M	2 yr.	..	Complete, except no glycosuria	Yes, cornea & marrow	
Hooft et al.[11]	F	7½ yr.	Yes	Only slight glycosuria	Yes	Bone marrow & lymph node
Dragsted & Hjorth [12]	M	49 yr.	No	Complete	No	Multiple myeloma 9 yr. after onset
Baber [13]	M	9 mo.	No	Complete	No	Autopsy: cirrhosis, normal parathyroids, little damage in kidneys
Engle & Wallis [14]	M	38 yr.	No	Complete	No	Multiple myeloma
Kretchmer [15]	F	4½ yr.	No	Complete	Yes, cornea & bone marrow	

* The "complete" Fanconi syndrome is resistant rickets (or osteomalacia), acidosis, glycosuria, amino-aciduria, organic-aciduria, and stunting.

sive renal damage has eventually occurred, resulting in renal failure and eventually death from uremia.

Whether the progressive renal damage results from a toxic effect of cystine,[3] a generalized disturbance in amino acid metabolism,[22] or a progression of renal disease on some other basis is uncertain. However, the pathogenesis of this progressive renal damage represents to us the core of the problem, and it must be solved before the longevity of children suffering from this disease can be significantly increased.

The purpose of this report is to present two cases of the Fanconi syndrome occurring in one family. The presence of cystinosis in both cases was diagnosed during life by the demonstration of typical cystine crystals in the bone marrow and cornea. Certain metabolic studies on these children will be presented with a critical discussion of our observations in light of the recent literature.

Report of Cases

CASE 1.—A boy was born on May 27, 1949, by an uneventful delivery after a full-term uncomplicated pregnancy. The birth weight was 7 lb. 3 oz. His mother and father, aged 25 and 34, respectively, were both in good health and were not related. An older brother, aged 4, was in good health.

Although the patient's neonatal course was otherwise normal, it was soon noted that his growth was somewhat slow. His parents' records indicated that he was always smaller than other children of comparable age, but his early motor development was normal and he seemed to be of normal intelligence. Within the first few months of life his mother noted that he became irritable, fussy, and wakeful at night and seemed to put out an excessive amount of urine, which turned brown on the diaper if allowed to stand and which to her, a nurse, had a "peculiar odor." Even as a tiny baby he had excessive thirst and would take an almost unlimited amount of fluid if it was offered. He tolerated heat poorly and perspired excessively, even with only a moderate elevation of environmental temperature. There was a marked tendency toward constipation. His appetite was capricious, and he always preferred liquids to solids. His diet consisted of large amounts of whole milk each day and variable amounts of solid foods of adequate variety. He received a full glass of orange juice and 10 drops of percomorph-liver oil (Oleum Percomorphum) per day for vitamin supplementation.

His motor development after the age of 6 months was slow. He sat alone at 10 months and did not walk until 18 months. His dentition was delayed, the first teeth appearing at 18 months. He was seen by a pediatrician at 16 months of age, and the parents were told that he was normal and that his urine examination was negative. However, when he did walk his gait was abnormal, being characterized as a "duck waddle." He walked with a wide base and marked external rotation of

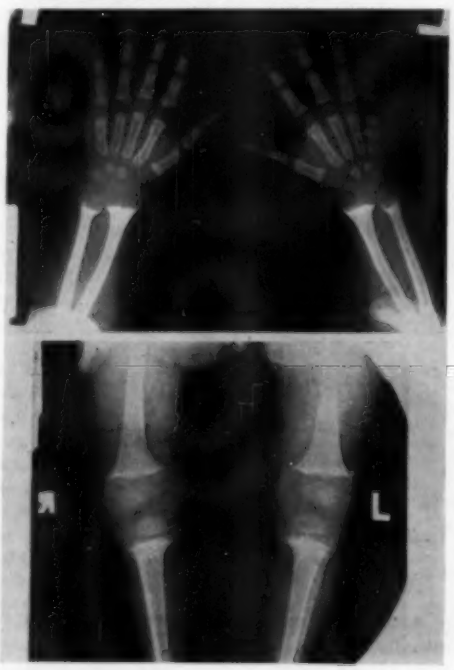
Fig. 1 (Case 1).—Patient at 2 years of age. Enlargement of the wrists and knees and costochondral beading are present.

the feet. Because of his abnormal gait, he was seen by an orthopedic surgeon, who made a diagnosis of rickets on x-ray examination and increased the percomorph-liver oil to 30 drops per day. Urinalysis revealed 4+ sugar, 4+ albumin, and many casts. He was treated as having renal rickets with diabetes for about six months. At the age of 2 years, blood chemistry studies revealed a normal blood sugar and a normal NPN. The calcium was 10 mg. per 100 cc., and the phosphorus, 2.6 mg. per 100 cc. Because of these findings and the persistent glycosuria and albuminuria, he was referred to the University of Minnesota Hospitals for investigation and treatment.

Physical examination on the first admission (June, 1951) revealed a white boy who was very small for 2 years of age: length, 78 cm.; weight, 9.5 kg. (both below 1 percentile for a normal 2-year-old boy.) He presented moderate but definite rachitic stigmata: costochondral beading, flaring of the costal margin, Harrison's groove (slight), and widening of the wrists and knees. Only 12 teeth were present. His gait was waddling, and there was marked abduction of the feet. The abdomen was slightly protuberant, and the liver edge was palpable 2 to 3 cm. below the right costal margin in the midclavicular line. His pulse rate was 120 per minute, and his blood pressure was 100/60. Aside from his small size and the moderate rachitic signs, there were no other positive physical findings. He did not appear to be ill and was alert, active, and intelligent. Figure 1 shows this patient at the age of 2 years. The characteristic external rotation of his feet, the large knobby knees, the costochondral beading, and the enlargement of the wrists are apparent in this photograph.

Routine studies of the blood were normal. His urine had a specific gravity of 1.015 and a pH of 5. The albumin was reported as 1+ and the sugar as 2+. There was a trace of acetone but no diacetic acid. A moderate number of finely granular casts were seen, but no red or white blood cells were present. The routine urine examinations remained essentially unchanged throughout the entire clinical course, showing persistent albuminuria, glycosuria, and cylinduria. The initial blood chemistry studies revealed the BUN to be 9 mg. per 100 cc.; the fasting blood sugar, 67 mg. per 100 cc.; CO_2-combining power, 14 mEq. per liter, and serum chloride, 110 mEq. per liter. Total serum protein was 7 gm. per 100 cc.; serum calcium was 11.3 mg. per 100 cc., and serum inorganic phosphorus was 3 mg. per 100 cc. The alkaline phosphatase was 41.1 King-Armstrong

Fig. 2 (Case 1).—Roentgenograms at 2 years of age, showing active rickets.



units. X-rays of the extremities showed active, moderately severe rickets (Fig. 2). X-rays of the abdomen showed no renal calcification. Because of the findings of stunted growth, hypophosphatemic vitamin D-resistant rickets, polyuria, polydipsia, renal glycosuria, and acidosis, a presumptive diagnosis of Fanconi's syndrome was made. The clinical diagnosis was confirmed by the demonstration of renal amino-aciduria and organic-aciduria in the course of our subsequent studies.

The patient was given 30 drops of percomorph-liver oil and 2 gm. of sodium bicarbonate daily in an attempt to reduce the acidosis and speed calcification of the long bones. He followed this regimen at home, after discharge from the hospital.

He was readmitted six weeks later for evaluation of the sodium bicarbonate treatment. Physical findings were essentially unchanged, except for a moderate improvement in his gait. X-rays showed evidence of calcification of the osteoid tissue. However, the blood concentrations of calcium and phosphorus were not improved and, in spite of the alkali therapy, the CO_2 was only 13 mEq. per liter and the Cl, 111 mEq. per liter.

Because of the failure of this regimen to control the acidosis and chemical rickets, the patient was given Shohl's citric acid-sodium citrate mixture.† He was given 90 cc. per day (supplying 90 mEq. of Na per day), and the dose of vitamin D was increased to 50,000 units per day.

He was admitted to the hospital a third time after five months of the above regimen. X-rays showed marked, although not complete, healing of the rickets, and the blood chemistry studies indicated slight improvement in the "chemical rickets" (calcium, 11.3 mg. per 100 cc.; phosphorus, 3.5 mg. per 100 cc.; alkaline phosphatase 40 King-Armstrong units) and moderate improvement in the acidosis (CO_2 21 mEq. per liter and chloride 107 mEq. per liter).

He continued the same regimen until his final admission, in May, 1952. During this period there was evidence of continued healing of the rickets by x-ray and improvement in the chemical rickets. The calcium remained normal, and the phosphorus returned toward normal. There was also improvement in his acid-base balance, with a rise in CO_2 content and a slight fall in chlorides. However, we were disturbed to find on his fourth admission that his serum calcium had risen to 17.1 mg. per 100 cc. (two determinations), with a phosphorus of 4.2 mg. per 100 cc. and an alkaline phosphatase of 20.1 King-Armstrong units. Roentgenograms taken at this time revealed no soft tissue calcification and showed complete healing of the rickets (Fig. 3).

† Sodium citrate, 98 gm.; citric acid, 140 gm.; distilled water to make 1000 cc.

Fig. 3 (Case 1).—Roentgenograms at 3 years of age, showing complete healing of the rickets after treatment with vitamin D and sodium citrate.

All vitamin D and citrate therapy was immediately discontinued, and the patient was given a low-phosphorus low-calcium diet with aluminum hydroxide (Amphojel), in an attempt to bring his serum calcium back toward normal and prevent metastatic calcification. He refused the diet, but his fluid intake remained good.

The patient appeared to be doing very well. He was active and happy and ran about on the ward in a nearly normal manner. He developed an upper respiratory infection a few days after admission, but he had no other abnormal findings until one week after admission, when he was noted to be pale and hypotonic. Blood chemical determinations on this day revealed calcium of 13.6 mg. per 100 cc. and phosphorus of 3.75 mg. per 100 cc., with alkaline phosphatase of 12.4 King-Armstrong units. He was not dehydrated, and there had been no increase in acidosis according to either clinical

or chemical criteria. However, two days later he had become dehydrated and was therefore given a whole blood transfusion and parenteral fluids. Despite energetic treatment with a lactate-saline hydrating solution (without potassium), the patient continued to manifest evidence of dehydration and acidosis, and 10 days after admission he had a sudden episode of gasping respirations and cyanosis and died. Shortly before death the BUN was 20 mg. per 100 cc.; CO_2-combining power, 8 mEq. per liter; chloride, 108 mEq. per liter; sodium, 130 mEq. per liter, and potassium, 3.8 mEq. per liter.

CASE 2.—A brother of Patient 1 was born on April 7, 1951, by a normal delivery following a normal pregnancy. His neonatal course and development were normal. He was given an evaporated milk formula and 12 drops of percomorph-liver oil daily. The only abnormality noted during his first six months of life was an odor of the urine which the mother said was similar to that of his older brother. An x-ray taken at 3 months of age was considered to be normal. When he was 7 months of age a routine urinalysis showed 1+ albuminuria and 1+ glucosuria. Because of these changes, he was referred to the University of Minnesota Hospitals for evaluation.

Physical examination on his first admission (Nov. 19, 1951) revealed no rachitic stigmata. He was active, sat alone, and could roll over both ways. His size and weight were normal for his age (7 months). The only abnormalities found were hypospadias and a chordee deformity of the penis.

The routine hemogram was normal. His urine had a specific gravity of 1.023 and a pH of 5. The albumin was reported as 1+, urine sugar as 2+, and acetone as 1+. No cellular elements were present. (In later specimens a variable number of granular casts have been reported.) The albuminuria, glucosuria, and acetonuria have been virtually constant. Blood chemistry studies during his first admission revealed BUN that varied from 7 to 13 mg. per 100 cc., fasting blood sugar of 60 and 85 mg. per 100 cc. on two determinations, CO_2-combining power of 20 mEq. per liter, serum chloride of 102 mEq. per liter, serum calcium of 10.4 mg. per 100 cc., and serum inorganic phosphorus that varied from 2.8 to 4.4 mg. per 100 cc. The serum alkaline phosphatase was 26 King-Armstrong units. X-rays of the knees, wrists, and elbows were negative.

The diagnosis of Fanconi syndrome was proved in this patient also by the findings of aminoaciduria, organic-aciduria, renal glycosuria, and chemical rickets. His initial treatment consisted of 2500 units of vitamin D and 25 cc. of Shohl's citric acid-sodium citrate mixture daily.

During the period between his first and second admissions there was little improvement in his laboratory findings but he continued to do well symptomatically. He gained weight steadily and began to walk without support or abnormality in gait.

He was admitted to the hospital in May, 1952, for metabolic study and repair of the hypospadias and chordee. This admission corresponded to the fourth and final admission of the patient's brother. Physical findings were unchanged from those of the previous admission, but blood chemistry studies revealed severer acidosis and the chemical features of rickets. His CO_2 was 20 mEq. per liter; chloride was 114 mEq. per liter; calcium, 10.3 mg. per 100 cc., and phosphorus, 2.7 mg. per 100 cc. His alkaline phosphatase had risen to 37.2 King-Armstrong units. There was no x-ray evidence of rickets.

He was admitted to the University Hospital for the third time in August, 1952. He had done well until six weeks prior to admission, when his mother noticed that he had developed a waddling gait similar to that shown earlier by his older sibling. Physical examination revealed slight costochondral beading and enlargement of the wrists and knees. The x-ray changes were characteristic of early rickets (Fig. 4). The serum calcium was within the normal range; the phosphorus was still low, and the alkaline phosphatase had risen to 54.7 King-Armstrong units. The CO_2 was 20 mEq. per liter, and the chloride, 109 mEq. per liter.

We felt that the development of overt rickets and the continued acidosis indicated a need for larger amounts of base and vitamin D, as well as the addition of potassium to the regimen. The patient was offered a mixture of sodium citrate and potassium citrate,‡ 15 cc. per day (supplying 50 mEq. of cation). He was given 10,000 units of calciferol (vitamin D_2) in addition to his ordinary vitamin supplement in an attempt to speed the healing of his rickets. One month after discharge, laboratory studies at another hospital showed improvement. The calcium was 10.3 mg. per 100 cc.; the phosphorus was 3.5 mg. per 100 cc., and the alkaline phosphatase was 10.5 Bodansky units. There was no improvement, however, in the acidosis; the CO_2 was 19 mEq. per liter, and the chloride was 106.8 mEq. per liter.

At this time the excess vitamin D was discontinued and the citrate mixture was continued as before. Two months later the calcium was 9.9 mg. per 100 cc. and the phosphorus was 3 mg. per 100 cc.; CO_2 was 14.5 mEq. per liter, and chloride, 113 mEq. per liter. Because of these changes, the dosage of the sodium and potassium citrate mixture was increased to 22.5 cc. (75 mEq. of base per day) and the vitamin D was resumed at a dose of 10,000 units per day.

‡ Na citrate, 68 gm.; K citrate, 62 gm.; water to make 350 cc.

Fig. 4 (Case 2).—Roentgenogram at 16 months of age. The presence of early rickets is apparent for the first time.

His fourth admission was in February, 1953, two and one-half months after beginning the above regimen. In spite of the high doses of base, the CO_2 content on admission was 11 mEq. per liter and the chloride was 107 mEq. per liter. The serum calcium was 10.4 mg. per 100 cc., and serum inorganic phosphorous was 2.4 mg. per 100 cc. X-rays indicated slight improvement in the rickets.

Because of the severity of the acidosis, the citrate mixture was increased to 45 cc. daily. Five days later, the CO_2 had risen to 22 mEq. per liter. However, at the time of discharge, 12 days later, the CO_2 was 20 mEq. per liter and the chloride was 110 mEq. per liter, even though he had received 150 mEq. of sodium and potassium daily.

He was treated with 10,000 units of vitamin D and 45 cc. of the citrate mixture daily for the following four months. Neither the acidosis nor the rickets were improved. In addition, he was given 15 cc. of a preparation containing tricholine citrate and inositol (Wychol) daily in the hope that the choline might have an inhibitory effect on the cystinosis.[185] No effect could be demonstrated. The citrate mixture was later increased to 200 mEq. per day without noticeable improvement. X-rays in April, 1954, showed severer rickets (Fig. 5).

He was readmitted in August, 1954, in order to try a much larger dose of vitamin D. Blood chemistry studies were unchanged, and x-rays showed active rickets. The patient was given

Fig. 5 (Case 2).—Roentgenograms at 3 years of age. Severe rickets is now present, in spite of large doses of vitamin D and citrate.

100,000 units of vitamin D daily, and the citrate mixture was discontinued. With this therapy, the x-rays became nearly normal (Fig. 6), the phosphorus rose to 4 mg. per 100 cc., the calcium remained normal, and the acidosis became no worse. (CO_2 stayed at 21 mEq. per liter; pH remained at 7.37 to 7.38). However, the serum potassium fell to 3.5 mEq. per liter.

He was discharged with directions to take 50,000 units of vitamin D and small doses of sodium and potassium citrate.

Two months later, the serum calcium was 14.3 mg. per 100 cc. and the serum inorganic phosphorus was 3.3 mg. per 100 cc. The phosphatase had fallen to 21 King-Armstrong units, and the x-rays showed intense calcium deposition in the zone of provisional calcification. During this admission, the 24-hour excretion of glucose and amino acids was markedly reduced in comparison with previous values. The acid-base balance remained in the same range, despite a much smaller dose of citrate solution.

Figure 7 shows Patient 2 at 3 years of age, compared with a 3-year-old child who is exactly at the norm for his age. The characteristic dwarfism, fair skin, and blond hair associated with this syndrome are evident.

Vitamin D dosage has been adjusted on the basis of the laboratory findings. With this variable dose of vitamin D, and added sodium and potassium citrate, he has continued to do well clinically. His development is normal, except that his height remains low for his age. Recently he has begun to excrete an excessive amount of urine, which has a relatively fixed specific gravity.

His laboratory findings have not maintained the initial good response from vitamin D. He remains in borderline acidosis; his serum potassium is always at the lower limit of normal, and the serum inorganic phosphorus cannot be raised without producing hypercalcemia. He has continued to have moderate glycosuria and amino-aciduria.

Summary of Clinical Findings and Courses.—Both of our patients with the Fanconi syndrome developed acidosis and rickets at an early age.

Patient 1 failed to respond until very large doses of vitamin D and base were given. After the rickets had healed, the large dose of vitamin D caused hypercalcemia. Death occurred during the course of an upper respiratory infection and appeared to be due to an electrolyte disturbance in which hypopotassemia, hypercalcemia, and acidosis were the prominent features.

Patient 2 has done very well clinically except for moderate dwarfism and minimal rachitic stigmata. Although there was x-ray evidence of healing of the rickets, the chemical abnormalities of rickets persisted until massive vitamin D therapy was used. The acidosis has been extremely resistant to therapy. The plasma bicarbonate remained low in spite of enormous doses of sodium and potassium. After intensive vitamin D therapy was begun, the acidosis improved and the amount of extra cation needed to keep the serum bicarbonate within the normal range was sharply reduced.

Fig. 6 (Case 2).—Roentgenogram at 3½ years of age. The radiological evidence of rickets has nearly disappeared, following massive vitamin D therapy.

Specific Studies Bearing on the Fanconi Syndrome

The characteristic biochemical abnormalities of the Fanconi syndrome were studied in both patients to verify the renal nature of the glycosuria and amino-aciduria and to investigate the cause of the rickets and acidosis.

In Case 2 these abnormalities were studied with clearance methods, in an attempt to define more clearly the renal origin of the dysfunctions.

Glycosuria.—Both patients had glycosuria, which was almost constant and of significant degree (2 to 10 gm. per day in Case 1; up to 15 gm. per day in Case 2). Fasting blood sugar levels were always normal, indicating that the glycosuria was renal in origin. Glucose-tolerance tests were normal in both patients.

Fig. 7 (Case 2).—Patient at 3 years of age (left), with a normal-sized 3-year-old boy. Moderate stunting and fair hair and skin can be seen.

The urine sugar in both patients was determined chromatographically § and was shown to be almost entirely glucose with a small amount of fructose (less than 5%).

Amino-Aciduria.—The most accurate method for determining the presence of hyper-amino-aciduria is the measurement of the free urinary α-amino nitrogen excretion by the ninhydrin-carbon dioxide technique of Van Slyke et al.[57] Normal values in children have been established by Childs,[58] who found the mean excretion to be 1.15 mg. per pound per day, with a high of 2 mg. per pound per day. These values agree fairly well with those found in normal adults by Frame and Rousch[59] and by Thompson and Abdulnabi,[60] using the same methods.

We have therefore assumed 5 mg. per kilogram per day to be the upper limit of normal for free α-amino nitrogen excretion when the ninhydrin-carbon dioxide method is used.

Both of these patients had hyper-amino-aciduria according to this standard. Patient 1 excreted from 37.8 to 45 mg. per kilogram per day (389 to 464 mg. per day). At 7 months of age, Patient 2 excreted on two occasions 29 mg. per kilogram per day (178 and 176 mg. per day). At 3 years of age, he excreted from 47 to 54 mg. per kilogram per day (600 to 700 mg. per day).

Plasma α-amino nitrogen levels were determined in both children by the method of Hamilton and Van Slyke.[61] The normal range for this determination is 3 to 5 mg. per 100 cc. In both patients normal values were found (Case 1, 4.1 mg. per 100 cc., and Case 2, 3.5 mg. per 100 cc.), indicating that the amino-aciduria as well as the glycosuria was renal in origin. During clearance studies in Case 2 plasma α-amino nitrogen was determined 13 times, and the only elevated values were those obtained during amino acid infusion.

Studies of individual amino acid excretion were carried out in both children by filter-paper chromatography, with use of methods similar to those of Dent.[62,63] When a consistent volume of urine was applied to the paper, more than 10 amino acid spots were detected each time, in contrast to the 3 or 4 spots from a normal person's urine.

Chromatograms done this way are actually semiquantitative, since the increased number of amino acids reflects the total increase of amino acids rather than a specific increase in the amino acids demonstrated. If a volume of urine is used which represents the same quantity of α-amino nitrogen, the chromatograms of normal persons and patients with generalized amino-aciduria are more nearly alike. Paper chromatograms of the urine from our patients by this latter method were essentially the same as those from the normal controls. The only consistent difference was that taurine was absent in both patients and present in all the normal controls.

§ Dr. Fred Smith, Professor of Biochemistry of the University of Minnesota School of Agriculture, made these determinations.

TABLE 2.—*α-Amino Nitrogen Excretion in Fanconi Syndrome* *

	Free Urinary α-Amino Nitrogen Excretion			
	Case 2		Normal Adult	
	% of Total	Mg./Day	% of Total, Mean (Range)	Mg./Day, Mean (Range)
Amino acid peak				
1. Leucine-isoleucine	4.3	7.7	2.7 (2.2–3.4)	3.3 (3.1–3.8)
2. Valine	2.3	4.1	1 (0.6–1.3)	1.2 (0.9–1.4)
3. Tyrosine-methionine	3.4	6.1	2.2 (1.5–2.8)	2.6 (2.0–3.0)
4. Alanine	9.8	17.6	5.8 (5.5–6.2)	7.4 (5.7–8.9)
5. Threonine-taurine	16.5 †	29.7 †	12 (6–23)	14.8 (8.1–22.0)
6. Serine	12.8	23	6.9 (5.2–9.0)	8.5 (7.5–9.6)
7. Glycine-glutamine	34.7	62.5	41 (30–50)	53.1 (29–69)
8. Lysine-"prelysine"	6.3	11.3	9.4 (6.4–11.6)	12 (8.4–16)
9. Histidine	7.7	13.9	16.1 (13–21)	20.8 (11–28)
Total	97.8	175.9	97.1	123.7 (75.7–171.7)
mg./kg./day		29		2.1 (1.36–3.2)
mg./sq. m./day		528		83
Total α-amino nitrogen excretion		179		128 (88–182)

* Modified from Frame and Rausch.[10]
† Since Taurine is absent from the patient's urine, this peak represents only threonine.

Paper chromatograms can be roughly quantitated to demonstrate the increased excretion of any one amino acid in comparison to the others. However, a more satisfactory method is the quantitative determination of individual amino acids in the urine, with use of either microbiologic assay or quantitative chromatography from a column.

Quantitation of the individual urine amino acids of Patient 2 was performed || by quantitative chromatography, with use of elution analysis from a starch column, as introduced by Stein and Moore.[64] The results are shown in Table 2. The amino acids form nine concentration peaks, some of which are made up of more than one amino acid. Although complete separation of the amino acids is not obtained, column chromatography is the most accurate method available for demonstrating the urinary amino acid pattern.

This patient demonstrated a relatively high concentration of the hydroxy-amino acids serine and threonine, which together make up 30% of the total amino nitrogen, and a reduction in the concentration of glycine-glutamine, lysine, and histidine. After hydrolysis of the urine the rise in α-amino nitrogen was only 25%, whereas in the normal person the rise is from 50% to 90%, which shows that Patient 2 excreted a larger percentage of his amino acids in the free form than does the normal person. The combined amino acid was made up chiefly of glutamic and aspartic acids. Almost no combined glycine was present.

These results indicate qualitative as well as quantitative abnormalities of urinary amino acid excretion and suggest that the reabsorptive defect may be greater for some amino acids than for others. However, these data are all from one 24-hour determination, and, since the amino acid excretion pattern may vary from day to day, the qualitative differences may not be of fundamental significance in this disease.

Organic-Aciduria.—Urinary organic acid excretion was measured by the titration technique of Van Slyke and Palmer.[65] The upper limit of normal for this determination is 1 mEq. per kilogram per day. Both patients had increased organic-aciduria by this method. Patient 1 excreted an average of 3.8 mEq. per kilogram per day, and Patient 2 excreted an average of 4 mEq. per kilogram per day. However, the normal value was obtained from persons without amino-aciduria, and, since amino acids increase the apparent value for organic acids, at least part of the increase in these patients is due to their hyper-amino-aciduria. Correcting the organic acids for the amino acid contribution is difficult, since the binding capacity of the amino acids varies, but a rough correction can be made by estimating

|| Performed and previously reported by Frame and Rausch.[10]

the molar concentration of amino acids from the α-amino nitrogen and using the average binding capacity of 0.4 mole HCl per mole of amino acid.[65] Subsracting the calculated amino acid contribution from the observed organic acid value reduces the nonamino organic acid excretion to 2.3 mEq. per kilogram per day in Patient 1 and to 3 mEq. per kilogram per day in Patient 2.

The frequently positive acetone reactions noted in these patients indicates that some of the nonamino organic acids are ketone bodies.

Estimation of the urinary organic acids by subtracting the measured anions from the sum of the cations paralleled the values obtained by titration, but the results are not quantitatively comparable, since sulfate was not determined.

The unmeasured anion fraction of the plasma was usually within the normal range in both patients, suggesting that the organic aciduria might be due to decreased tubular reabsorption of filtered organic acids rather than to an increased plasma level. However, since the organic aciduria was of only moderate severity, it remains a possibility that it might be attributable to an elevation of plasma organic acids too small to produce a detectable increase in the unmeasured anion fraction.

Acidosis.—Both patients had hyperchloremic acidosis which was resistant to therapy with "alkalinizing" salts. The serum bicarbonate was elevated by such therapy, but not to the extent anticipated in the presence of normal tubular mechanisms. CO_2 content even during therapy with excess base averaged 16.6 mEq. per liter in Patient 1 and 18.7 mEq. per liter in Patient 2. The highest CO_2 attained by either patient was 23 mEq. per liter.

It seems obvious that the organic-aciduria alone could not explain the acidosis; indeed, the organic acid excretion was much lower than that usually observed in patients with diabetes mellitus at comparable serum bicarbonate levels[65,66] and acidosis was present even when the organic acid excretion was only slightly above the normal value. We therefore investigated the possibility that the renal mechanism for conservation of base might be inadequate. Inadequacy of the renal tubular base-conserving mechanisms has been described previously in patients with the Fanconi syndrome.[7,19,22,31,43]

The urinary pH of Patient 1 varied from 5 to 6 prior to therapy. After therapy was started, the pH was always greater than 7, even when acidosis was present. The titratable acidity of the urine averaged 35 mEq. per square meter per day (normal value without acidosis, 5 to 20 mEq. per square meter per day; normal value with acidosis, up to 200 mEq. per square meter per day).[66,67] The ammonia excretion during spontaneous acidosis varied from 16 to 50 mEq. per square meter per day (normal value without acidosis, 20 to 30 mEq. per square meter per day; normal value with acidosis, from 70 to 150 mEq. per square meter per day).[66,67] With an ammonium chloride load, it rose to 60 mEq. per square meter per day.

Patient 2 had a urinary pH of 5 prior to therapy. Thereafter, it remained above 7. When ammonium chloride was given, the pH fell to 5.5. The titratable acidity of the urine averaged 34 mEq. per square meter per day. The urinary ammonia excretion averaged 40 mEq. per square meter per day. With ammonium chloride stimulation, it rose to 72 mEq. per square meter per day. However, on two occasions during severe spontaneous acidosis the ammonia excretion was more than 100 mEq. per square meter per day.

Calcium and Phosphorus Excretion.—Both patients had relative hyperphosphaturia, considering the low levels of serum phosphorus. In Patient 2, on whom we have more data, the urinary phosphorus excretion at various times during hospitalization was 800 to 1200 mg. per square meter per day. His urinary calcium excretion was 200 to 600 mg. per square meter

per day. Since his intake was never as great as that of a normal child, especially while he was in the hospital, these rates of excretion are interpreted to represent absolute phosphaturia and calcuria as well.[22] In the absence of data on the calcium and phosphorus balances, we cannot be sure whether the rickets results solely from the urinary losses or whether poor intestinal absorption may be a contributing factor. However, in Case 2, at least, the urinary loss would seem to be an adequate explanation.

Clearance Studies.—Specific kidney functions were measured in Patient 2, with use of standard clearance and excretion techniques. The clearance and reabsorption of the substances affected by the Fanconi syndrome were then studied, with use of the standard substances for comparison.

The initial studies were done at a time when the patient manifested rickets and acidosis. Vitamin D was discontinued three weeks prior to the studies, and the clearances were measured on three occasions, during which the patient received sodium and potassium citrate, sodium citrate alone, and ammonium chloride, respectively. The effects of glucose infusion and amino acid infusion were studied also.

The clearance studies were repeated seven months later, after the patient had been treated with 100,000 units of vitamin D daily for three weeks. They were repeated again after two months of treatment with 50,000 units daily.

Methods

Glomerular filtration rate was determined by inulin clearance, with use of a constant-infusion technique. Inulin in blood and urine was determined by the method of Bojesen.[68] "Specific" endogenous creatinine clearance was used as a measure of glomerular filtration rate when long collection periods were necessary. Creatinine was determined by the method of Miller and Miller.[69] The clearance of *p*-aminohippurate (PAH) was determined at low plasma levels, with use of a constant infusion of PAH. The maximal tubular secretory capacity for PAH (Tm_{PAH}) was determined at elevated plasma concentrations with a load/T ratio of $\left(2 \text{ load/T} = \frac{\text{amount delivered to tubule}}{\text{maximum secretory capacity}}\right)$. Filtered PAH was determined from the following formula: plasma level of PAH×filterable portion of PAH×inulin clearance. The filterable portion was assumed to be 0.83. PAH was determined by the method of Smith et al.[70] Arterial plasma glucose concentrations for the glucose clearance and glucose Tm were approximated by using blood obtained by finger puncture from a warmed extremity. Glucose was determined by the method of Nelson.[71] Venous blood was used for the measurement of plasma α-amino nitrogen and inorganic phosphorus, since an adequate amount of blood could not be obtained by finger puncture and the use of numerous arterial punctures at short intervals seemed too arduous. The α-amino nitrogen concentrations in plasma and urine were determined by the ninhydrin-CO_2 methods.[67,68] Phosphorus was determined by the method of Fiske and Subborow.[72]

Results

Table 3 lists the clearances, the Tm's for secretion or reabsorption, and the ratios of the clearances and Tm's to one another. The actual values are also corrected to the standard adult surface area, to facilitate comparison. Table 4 shows the changes which were found following massive vitamin D therapy.

The inulin and endogenous creatinine clearances determined from the same samples were nearly identical. The difference is less than the range of error of either method. Therefore, in this patient, the creatinine clearance may be considered an

TABLE 3.—*Renal-Function Studies in Case 2*

	Observed	Per 1.73 Sq. M.	Normal (per 1.73 Sq. M.)*	Fraction of Normal
A. Clearances (cc./min.)				
1. Inulin	31	98	123	0.80
2. Endogenous creatinine	31.97	100.7	123	0.81
3. PAH	78.3	246.6	630	0.39
4. Glucose	10.6	33.4	--	--
5. α-Amino N	5.7	18	2	9.0
6. Phosphorus	9.8	30.9	12	2.6
B. Tm (mg./min.)				
1. PAH	8.7	27.4	77.2	0.356
2. Glucose (load/T—1.5)	18	57	--	--
3. Glucose (load/T—6)	19.6	61.7	339	0.18
C. Ratios				
1. "Filtration fraction"	0.40	--	0.195	2.0
2. C_{In}/Tm_{PAH}	3.56	--	1.54	2.3
3. C_{In}/Tm_{G}	1.58	--	0.35	4.4
4. $C_{\alpha\text{-amino N}}/C_{In}$	0.22	--	0.01-0.03	10.0
5. C_{PO_4}/C_{In}	0.316	--	0.1	3.0
6. $T_{\alpha\text{-amino N}}/GF_{\alpha\text{-amino N}}$	0.8	--	0.98	0.82
7. TRP/GFP	0.67	--	0.9	0.74

* References 43 and 73-75.

TABLE 4.—*Response of Renal-Function Studies in Case 2 to Massive Vitamin D*

	Clearance, Ml./Min.	Filtered Load, Mg./Min.	Reabsorption, Mg./Min.	% Reabsorption
Before treatment				
α-Amino nitrogen	5.7	1.35	1.04	78
Phosphate	9.8	0.785	0.547	70
Glucose	10.6	29.0	19.4	67
Inulin	31.0			
PAH	78.3			
After treatment				
α-Amino nitrogen	0.7	0.58	0.507	88
Phosphate	7.0	0.76	0.492	65
Glucose	4.5	16.0	12.4	77
Inulin	20.0			
PAH	64.5			

accurate measure of the glomerular filtration rate. Seven months after the original studies the inulin clearance had fallen from 31 to 20 ml. per minute. Two months later the inulin clearance was still 20 ml. per minute.

The PAH clearance and the maximum secretory capacity for PAH showed approximately the same reduction from the normal. The PAH clearance cannot be considered to be a true measure of the renal plasma flow, because the inadequacy of the proximal tubules probably limits the rate of PAH removal so severely that PAH extraction is incomplete, even at low plasma levels.

A repeat PAH clearance determination nine months later revealed a decline of the PAH clearance from 78 to 69 ml. per minute. This decline could be explained by the decrease in filtered PAH as a consequence of the decreased glomerular filtration rate. The "tubular clearance of PAH" (that portion of the PAH clearance contributed by tubular secretion) remained essentially unchanged.

Glucose. The reabsorption of glucose was severely depressed. The tubular reabsorptive capacity was saturated even at endogenous loads, the load/T ratio being 1.5 at normal levels of plasma glucose. Infusion of glucose raised the load/T ratio to 6, without significantly increasing the amount of glucose reabsorbed, and so the amount excreted directly paralleled the amount filtered at all plasma levels. The infusion of glucose did not affect the amino acid or phosphate reabsorption.

Glucose excretion decreased after treatment (accompanied by a decreased insulin clearance). Glucose Tm was not determined, but the reabsorption at endogenous glucose levels was less than it had been before therapy.

Amino acids. The clearance of α-amino nitrogen was high at normal plasma levels and rose when amino acids were infused. The ratio of the amino acid clearance to the inulin clearance was approximately 10 times as high as normal.

The tubular reabsorption of amino acids was deficient even at low plasma levels. Only about 80% of the filtered amino acid was reabsorbed, in comparison with the normal of 98%.

The maximum tubular reabsorptive capacity for amino acids was not approached, since the plasma level was only moderately elevated by the amino acid infusion. Elevation of the plasma α-amino nitrogen from 4.49 to 6.93 mg. per 100 cc. increased the tubular reabsorption from 0.96 to 1.65 mg. per minute. The percentage reabsorption declined from 82% to 76%, and the clearance rose 50%.

Elevation of the plasma amino acid level had no effect on glucose or phosphate reabsorption.

A repeat amino acid clearance determination seven months after the original studies showed a marked decrease in the amino acid clearance and excretion. These decreases were accompanied by a reduction of the glomerular filtration rate sufficient to reduce the filtered load to less than one-half the amount reabsorbed per minute in the previous tests. Infusion of amino acids raised the filtered load to the level of the first test, and during these periods the calculated reabsorption was less than it had been during the initial test. Therefore, the decreased excretion was attributable to the lower filtration rate and not to improvement in tubular function.

Phosphate. Definite phosphaturia was present at low plasma phosphorus levels. The phosphate clearance of 31 cc. per minute per 1.73 square meters is abnormal at plasma levels of 2 to 3 mg. per 100 cc., especially in the presence of a reduced glomerular filtration rate. The ratio TRP/GFP (the fraction of filtered phosphorus which is reabsorbed), which should be nearly 0.9 when the plasma phosphorus level is this low, was only 0.67.

Treatment with large amounts of vitamin D for three weeks raised the serum inorganic phosphorus from 2.5 to 4.0 mg. per 100 cc., with only a slight rise in urinary phosphate excretion. The phosphate clearance fell to 6.6 cc. per minute (21 cc. per minute per 1.73 square meters).

The decrease in phosphate clearance coincided with the decrease in the glomerular filtration rate between the two test periods. Because of the low glomerular filtration rate, the amount of phosphorus filtered was less during the second test, even though the plasma level was higher. The phosphate excretion was slightly higher during the second test, and so the amount of phosphate reabsorbed and the percentage reabsorption TRP/GFP were actually less after vitamin D therapy. Two months later the phosphate clearance was essentially the same. The serum phosphorus was lower, and the urinary excretion was slightly lower. The ratio TRP/GFP had fallen slightly.

Bicarbonate. Bicarbonate clearance was high in the presence of a low plasma bicarbonate concentration and a reduced glomerular filtration rate, demonstrating reduced tubular reabsorption of bicarbonate.

Bicarbonate loading experiments were not performed on this patient, and so the maximum capacity of the tubules for bicarbonate reabsorption is unknown. However, from the data we obtained on the absorption at lower levels, we would conclude that the maximum reabsorbing capacity was probably reduced.

As Pitts et al.[76] have shown, bicarbonate excretion in the adult does not normally occur when the plasma level is less than 24 mEq. per liter. Above this level, excretion begins and rapidly increases as the plasma level is raised. However, reabsorption also continues to increase until the plasma level is approximately 28 mEq. per liter, above which the reabsorption is essentially constant at about 2.8 mEq/100 ml. of glomerular filtrate. The rapid saturation of the reabsorptive mechanism at plasma bicarbonate levels only slightly above the level at which excretion begins aids in keeping the plasma bicarbonate within narrow limits in the normal person.

The bicarbonate excretion and reabsorption were measured in this patient while he was receiving sodium and potassium citrate solution (plasma bicarbonate 19.4 mEq. per liter) and while he was receiving small doses of ammonium chloride (plasma bicarbonate 14.6 mEq. per liter.

When the plasma bicarbonate was 14.6 mEq. per liter, the patient excreted 0.0016 mEq. per minute (0.005 mEq. per minute per 1.73 square meters). This rate of excretion occurs in the normal adult at a plasma bicarbonate of approximately 24 mEq. per liter. The plasma bicarbonate of 14.6 mEq. per liter probably approaches the minimal level at which bicarbonate excretion occurs (bicarbonate was absent from the urine on another occasion when the serum CO_2 content was 11 mEq. per liter).

When the serum bicarbonate was 19.4 mEq. per liter, the patient excreted 0.05 mEq. per minute (0.15 mEq. per minute per 1.73 square meters). This rate of excretion does not occur in the normal adult until the serum bicarbonate is elevated to approximately 27 mEq. per liter. If the excretion is corrected to the normal filtration rate, rather than to the adult surface area, it corresponds to 0.2 mEq. per minute. At this level, the patient was reabsorbing bicarbonate at a rate of 1.8 mEq/100 ml. of glomerular filtrate (approximately 92% of the filtered bicarbonate). Since this rate of excretion occurs in the normal person only when the reabsorptive mechanism is al-

most saturated, it is likely that the tubular reabsorptive mechanism in this patient is nearly saturated when his plasma bicarbonate is about 20 mEq. per liter (at a glomerular filtration rate of 32 ml. per minute). It is unlikely, therefore, that bicarbonate reabsorption could rise much above 1.8 mEq/100 ml. of glomerular filtration. This conclusion receives support from the clinical observation that the serum CO_2 content stabilized at about 20 mEq. per liter each time the dose of alkali was increased.

The tubular reabsorption of bicarbonate has not been studied in children, and so no standards are available for comparing these results with those of the normal child. Since the serum bicarbonate is generally lower in children than in adults, the tubular reabsorption in this patient may not be depressed as much as the comparison with adults would indicate. However, even in infants the CO_2 content is maintained between 20 and 25 mEq. per liter, and so the lowest CO_2 content at which bicarbonate excretion normally occurs at any age is probably not less than 20 mEq. per liter. Therefore, we must conclude that the depressed reabsorption cannot be explained by the normal difference between children and adults.

Sodium, chloride, and potassium. The clearances of sodium, chloride, and potassium were measured on three occasions. The sodium and chloride clearances were normal each time. The potassium clearance was 40% of the inulin clearance during a period when extra potassium was being given. The clearance on the other occasions was only 15% of the inulin clearance. The excretion of sodium and potassium was high in comparison with that of the average child of the same age,[22] but the intake and the stool losses were not measured, and so this cannot be used as proof of excessive urinary loss. Therefore, we have no direct evidence that the urinary excretion of these electrolytes was abnormal in this patient.

Miscellaneous Laboratory Findings.—Total serum proteins, chemical fractionation, and electrophoretic patterns were consistently normal in both patients. In addition, all liver-function studies which were measured (direct- and indirect-reacting serum bilirubin, sulfobromophthalein retention, cephalin-cholesterol flocculation, thymol turbidity, total cholesterol, and cholesterol esters) were normal.

Summary and Interpretation of Investigations.—Both the routine clearances and the determinations of tubular reabsorption as a function of glomerular filtration demonstrate that the glycosuria, amino-acidura, phosphaturia, and "bicarbonaturia" represent a failure of tubular reabsorption. The severe depression of Tm_G and Tm_{PAH} demonstrate that the defect is diffuse, involving most of the tubules. The relatively normal glomerular filtration rate in the early phases of the disease shows that the function of the renal tubule is specifically altered at an early stage. The ability of the kidney to secrete ammonia when the stimulus is great enough and the normal ability to concentrate the urine indicate that only the proximal tubular functions are abnormal.

The decline of the glomerular filtration rate accompanying the decline in the clearances shows that decreased filtration rather than increased reabsorption was responsible for the reduced excretion of glucose, amino acids, and bicarbonate and the reduced clearance of phosphate following vitamin D therapy. The only important single source of error which might invalidate this interpretation is the inulin clearance, which is the basis for calculating tubular reabsorption. The clearance determinations have been carefully reviewed, and no obvious errors or anomalous results could be detected. The agreement between the periods of each study was adequate; the clearances were measured at the same time each day; the patient's diet remained essentially the same, and the clearances were determined enough times to become almost "routine" to this boy, and so emotional factors were minimized.

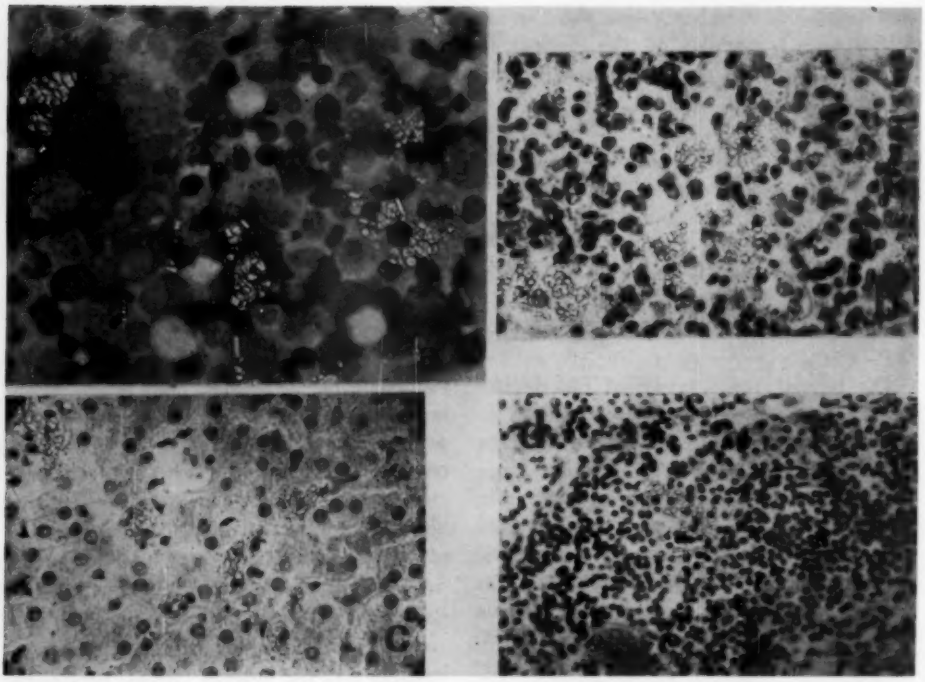


Fig. 8 (Case 1).—(*a*) Cystine crystals in a bone marrow preparation. (*b*) Cystine crystals in the spleen. (*c*) Cystine crystals in the liver. (*d*) Cystine crystals in a lymph node.

In addition, the decline in PAH clearance paralleled the fall in inulin clearance. If the decreased clearance of the other substances were attributable to improved tubular function, the PAH clearance would be expected to increase rather than decrease. Therefore, we feel that our interpretation of the response to vitamin D therapy is valid, even though it is contrary to the findings of others.[22,42]

Our data do not permit a definition of specific amino acid reabsorption defects. It is, therefore, not possible to say whether the reabsorption of any one amino acid is depressed more than that of another. However, these data do demonstrate that the amino-aciduria is generalized and suggest that the defect is of roughly the same magnitude for all amino acids.

The loading experiments do not support the concept that competition for reabsorption might explain the phosphaturia or amino-aciduria,[22] nor do they show any obligatory relation between glucose and amino acid excretion[2] except that imposed by the relative severity of the tubular defects.

Cystinosis: Examination of bone marrow aspirates from both patients revealed abundant cystine crystals in the reticuloendothelial cells. Examination of the eyes with the slit lamp revealed the cornea to be diffusely studded with cystine crystals. The appearance of the cystine crystals in material obtained from the bone marrow is shown in Figure 8*a*.

Autopsy Findings on Patient 1: The gross anatomy of all organs was normal, except for slight enlargement of the parathyroid glands. No crystals were seen grossly on cut section of any organ.

Microscopic examination showed yellowish crystals with an angular shape located in the spleen, liver, lungs, lymph nodes, bone marrow, and kidneys. (Figures 8*b*, *c*, and *d*

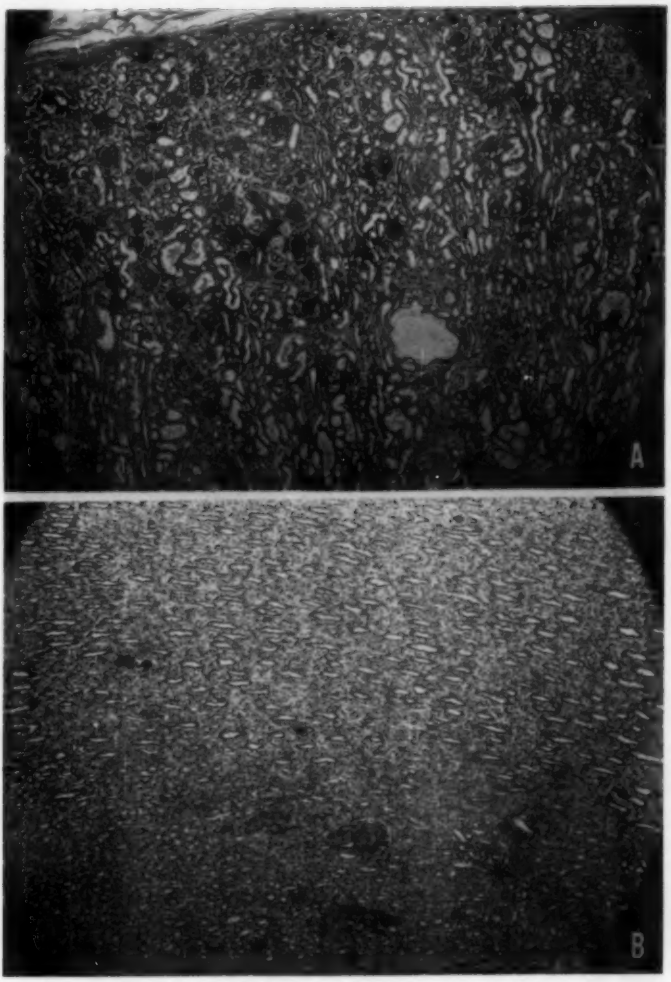


Fig. 9 (Case 1).—*A*, kidney cortex, showing dilatation and degeneration of the proximal tubules. The glomeruli appear normal. *B*, kidney medulla, showing granulomata.

show the characteristic appearance of the cystine crystals in the spleen, liver, and lymph nodes.) The cystine deposits occurred predominantly in the reticuloendothelial cells and in the cells of the supportive tissues of these organs. A few crystals were found outside the reticuloendothelial cells, but these were probably due to rupture of the reticuloendothelial cells during processing of the sections.

No abnormalities of the glomeruli were noted in any of the sections of the kidney. The proximal convoluted tubules showed changes varying from hydropic degeneration to tremendous dilatation of the tubules with flattening of the epithelium, giving a honeycomb appearance to the kidney sections (Fig. 9*A*). In the medulla there were a number of granulomata in which small deposits of calcium and a few cystine crystals were found (Fig. 9*B*). The basis of these latter lesions is uncertain; it is conceivable that either metastatic calcification or deposits of cystine might call forth a proliferative reaction such as this.

Consideration was given to the possibility that these granulomata might have produced the proximal tubular dilatation by obstruc-

tion of the tubules. However, no actual compression of the tubules could be demonstrated, and the granulomata appeared to be far distal to the dilated segments, rather than immediately distal to them, as would have been expected. In addition, the granulomata seemed too few in number to have caused the diffuse dilatation, which appeared to involve most of the proximal tubules.

The parathyroid glands were normal histologically.

In addition to the cystine deposits, the lungs showed thickening of some alveolar walls and edema fluid and hemorrhage in some alveoli. The rest of the organs, including the brain, were normal histologically. There was no indication of the cause of death from the postmortem examination.

Chemical determination of the electrolyte content of skeletal muscle (diaphragm) was carried out to see if any gross electrolyte abnormality was present. The results are presented in Table 5.

This analysis demonstrates a depression of intracellular potassium and magnesium concentration and an elevation of intracellular sodium and calcium concentration. These findings along with the clinical and laboratory findings force us to conclude that the cause of death was a combination of cellular potassium deficit and cellular calcium excess. An increase in calcium and a decrease in potassium concentration produce similar abnormalities, especially on the heart, and the result of the changes in these ions is therefore additive. The elevated intracellular sodium and decreased magnesium probably intensified the same effect. The severe acidosis may have been a contributing factor.

Microdissection of the kidneys was done to determine if the lesions described by Clay, Darmady, and Hawkins [78] were present in this case. The nephrons were extremely friable, the glomeruli breaking away from the proximal tubule very easily. In the few nephrons which were obtained intact, a lesion similar to the one described by Clay et al. was found: marked narrowing of the first portion of the proximal tubule with apparent shortening of the whole proximal tubule. However, the number of narrowed tubules demonstrated was small, and, since some narrowed tubules were observed in other types of renal disease, we could not consider this a characteristic anomaly from our findings. Inspection of the dissected nephron and careful scrutiny of serial sections of the kidney did not reveal the "swan's-neck" lesion which they described.

Microdissection confirmed the tubular dilatation seen on the routine sections. Whereas the narrowed area could be identified in only a few tubules, a dilated segment was present in every one isolated. The dilatation occurred close to the narrowed segment and appeared similar but not identical in all the tubules. The diameter in some was three times that of the glomerulus. The epithelial thinning of these areas in the sections suggested tubular obstruction, but the apparent regularity of the large area following an "atrophic" segment suggested they might represent an atypical work hypertrophy in the less severely involved portion of the tubule.

During the dissection it was noted that the tubules had a glittering appearance which was not present in the normal kidneys used for controls. The proximal tubule appeared to be coated with a substance which sparkled in reflected light. The nature of the substance is unknown, since chemical analysis could not be done in this preparation. One possibility is that it represents excess calcium in the tubular cells as a consequence of the hypercalcemia. The location agrees well with the location of tubular calcium deposits in experimental hypervitaminosis D.[79] However, the sparkling ap-

TABLE 5.—*Electrolyte Content of Skeletal Muscle (Diaphragm)*

	Electrolytes, mEq./Kg. Wet Weight of Tissue					
	P	Ca	Mg	Na	K	H_2O, Ml.
Case 1	47.4	13.1	7.4	54.6	55.1	753
Normal [77]	66	3.2	18	28.7	97	730

pearance of the substance suggests that it might consist of cystine crystals in or on the periphery of the tubular cells.

Comment

The two cases presented in this report are typical examples of the Fanconi syndrome with cystinosis. The symptoms, physical findings, and chemical changes are all similar to those of the majority of the reported cases. We therefore feel confident in generalizing from these cases and in drawing conclusions from the data of others when our own are insufficient.

Since the first reports of the Fanconi syndrome [80-82] and cystinosis [56,83,84] were published, a tremendous mass of conflicting facts and an even greater mass of conflicting interpretations have been published about the Fanconi syndrome and cystinosis. The two areas of greatest controversy have been the physiologic and chemical abnormalities responsible for the clinical features of the Fanconi syndrome and the relationship between the Fanconi syndrome and cystinosis.[85]

Fanconi's original hypothesis was that the syndrome of glycosuric rickets resulted from an excessive loss of phosphorus, fixed base, and glucose in the urine. He suggested that the loss of these substances was due to a renal lesion which interfered with reabsorption in the proximal tubule.

After the discovery that the syndrome was almost invariably associated with cystinosis, many authors [1,8,86] considered the primary abnormality to be a disturbance in the deamination of amino acids, manifested by an accumulation of cystine in various organs. The disturbed protein metabolism was held responsible for most of the observed abnormalities. The amino-aciduria was ascribed to spillage into the urine because of an elevated blood level; the organic-aciduria and acidosis, to the presence of organic acid residues of improperly deaminated amino acids, and the stunting, to protein deficiency. At that time, cystinosis and cystinuria were generally considered to be variants of the same disease.[87]

Renal dysfunction was not considered important in the initial pathogenesis of the syndrome, and the later renal insufficiency which invariably occurred was considered to be due to the toxic action of accumulated cystine.

Later, Dent [63] and others [7,12,30] demonstrated that the plasma amino acid level was normal and concluded that the amino-aciduria, as well as the glycosuria and phosphaturia, was of renal origin. These findings reaffirmed Fanconi's original theory, and suggested that most of the clinical findings could be explained by the tubular abnormality.

However, in 1952, Bickel et al.[22] again suggested that a disorder of protein metabolism produced both the cystinosis and the clinical abnormalities. They cast doubt on the tubular reabsorption theory to explain the urinary findings. In an extensive study, this group found an elevation of some plasma amino acids, using chromatographic and microbiologic methods, and considered the elevated blood levels to be responsible for the amino-aciduria. They also found reduced intestinal absorption of calcium and phosphorus and felt that poor absorption, rather than increased urinary excretion, was the cause of the rickets. Renal glycosuria was present in all their cases, but they suggested that the cause might be formation of glucose from amino acids by the kidneys rather than failure of glucose reabsorption.

These authors advanced the theory that the primary disturbance was a quantitative insufficiency of protein anabolism, centered chiefly in the reticuloendothelial cells. The partial failure of amino acid utilization causes them to accumulate in those tissues. Cystine, because of its insolubility, precipitates as crystals which are visible on microscopic examination. According to this theory, the other amino acids are presumably present in excess also but are not visible because they do not precipitate.

Although this theory has gained wide acceptance,[36,45,55,88] many other investigators [42,43,49,89-91] have considered an abnormality of the renal tubules to be the chief cause of the chemical and physiological abnormalities that make up the Fanconi syndrome. The latter opinion has been substantiated by the present study. Our findings indicate that deficient tubular reabsorption is responsible for the glycosuria, aminoaciduria, phosphaturia, and acidosis.

The reduced tubular reabsorption of glucose and the failure of the reabsorption to increase significantly when the plasma glucose is elevated show that the reabsorptive mechanism is grossly inadequate. The simultaneous rise in urine glucose as the plasma glucose is elevated demonstrates that the plasma glucose is the immediate source of the urine glucose and obviates the theory that glucose is formed by the kidney.

Amino acid reabsorption is more difficult to study than glucose reabsorption, because many substances are involved which are reabsorbed at various rates by the renal tubules. Our evidence that the aminoaciduria is due to reduced reabsorption is, therefore, less definitive, because of this complexity and because the methods we used to study the amino acid excretion were quantitatively less exact.

However, the difference in amino acid reabsorption between these patients and the normal is so clear-cut that there can be little doubt that the abnormality resides in the renal tubule. It is unlikely that any significant change in interpretation will result from studies of individual amino acid clearances.

The normal plasma amino acid levels found in our patients and in most other patients with the Fanconi Syndrome [2,7,8,12, 27,30,33,42,43,49] not only substantiate the renal origin of the amino-aciduria but also cast strong doubt on the theory that a defect in protein metabolism underlies the Fanconi syndrome and cystinosis, since this theory was based on the assumption that the plasma amino acid level is increased.

Hyperphosphaturia and hypophosphatemia are constant features of the early stage of the Fanconi syndrome. There is general agreement that the phosphorus clearance is abnormally high and that the high clearance is due to reduced tubular reabsorption. However, there is disagreement concerning whether the reduced reabsorption is caused by an intrinsic tubular anomaly or by secondary hyperparathyroidism.

The results reported here demonstrate that the phosphaturia is due to a renal tubular defect which is not amenable to treatment with vitamin D and, therefore, presumably not due to secondary hyperparathyroidism.

This conclusion is further supported by the finding that the serum calcium in both patients of this report rose above the normal value without bringing the serum phosphorus up to normal, at a time when the bones appeared well mineralized on x-ray. The rise of the serum calcium should have exerted enough inhibitory effect on the parathyroids to normalize the serum phosphorus if hyperparathyroidism had been the causative factor.

In addition, the experimental production of the Fanconi syndrome is characterized by an immediate phosphaturia, which is intensified by prior treatment with vitamin D.[92] This response can be explained only by a direct effect on the tubules, since the time factor excludes the possibility of a secondary effect on the parathyroids.

We have found no case reports in which parathyroid hyperplasia was demonstrated during the hypophosphatemic stage.

However, other evidence suggests that secondary hyperparathyroidism may also occur. Improved phosphate reabsorption following vitamin D therapy has been reported.[31] The patient reported by Linder et al.[7] had hyperphosphatemia before the hypophosphatemia began. This implies parathyroid control over the serum levels and strengthens the possibility that the parathyroids may determine the serum phosphate level in other cases.

Therefore, it is likely that increase parathyroid activity contributes to the phosphaturia in some patients. The stimulus for hyperparathyroidism might be either acidosis [93] or decreased calcium absorption from the gastrointestinal tract.[22]

The acidosis of the Fanconi syndrome is due to the combination of organic-aciduria and partial failure of the kidney to conserve fixed cations in the normal manner.

The excess urinary excretion of organic acids produces a loss of the cation with which they are combined. Whether the cation lost is "fixed cation" (chiefly sodium) or "dispensable cation" (hydrogen and ammonium) depends on the ability of the kidney to replace the fixed cation in the glomerular filtrate with hydrogen or ammonium. The loss of cation, therefore, depends both on the severity of the organic-aciduria and on the extent to which the organic anions are excreted as the salt rather than the acid.

The cause of the organic aciduria is still not certain. The most probable cause is a partial failure of reabsorption by the tubules. The organic acids, including the "ketone bodies," are threshold substances and are normally almost completely reabsorbed at the usual plasma levels.[94,95] The reabsorption of the organic acids is, therefore, an active process, dependent on tubular function in much the same way as is the reabsorption of the other metabolites, glucose, and amino acids. The presence of the other reabsorption defects suggests that the organic acid-reabsorbing mechanism may also be defective. The absence of a rise in the unmeasured anions of the plasma in our cases adds support to this possibility.

However, ketonemia with overflow ketonuria may contribute, during periods when the food intake is curtailed, in a manner similar to that which occurs in isolated renal glycosuria.[96] The glycosuria stimulates gluconeogenesis by producing a tendency toward hypoglycemia, and when anorexia or infection is superimposed the reduction in glycogen reserves may increase gluconeogenesis sufficiently to produce ketosis.[97]

The more important cause of acidosis is the failure of the renal tubules to reabsorb enough fixed cation from the glomerular filtrate. This is manifest directly by deficient bicarbonate reabsorption and indirectly by the "relative deficiency" of ammonia and titratable acid in the urine. The impaired bicarbonate reabsorption allows bicarbonate to escape into the urine along with cations derived from the plasma. Of course, it is the loss of the cation which is important, but the bicarbonate serves as a convenient measure of the amount of cation wasted.

The mechanism of bicarbonate reabsorption is still not well understood. The response to carbonic anhydrase inhibition indicates that all of the processes the kidney uses to prevent acidosis, including bicarbonate reabsorption, are controlled by the hydrogen ion exchange mechanism.[98] This mechanism functions by replacing the sodium ions in the glomerular filtrate with hydrogen ions. The tubular cell reabsorbs sodium and secretes hydrogen to take its place in the urine. This converts the sodium bicarbonate of the filtrate to carbonic acid. After the carbonic acid is dehydrated, the CO_2 diffuses into the cell. The net result is the same as if sodium bicarbonate were reabsorbed directly.

By the same mechanism, dibasic phosphate and the salts of organic acids are converted into monobasic phosphate and free organic acids, respectively. Unlike carbonic acid, however, they are not diffusible and so remain in the urine and contribute to titratable acidity. The hydrogen ions are derived from carbonic acid, which is formed in the cell from metabolic CO_2 under the catalytic influence of carbonic anhydrase, and so the efficiency of the exchange depends on the activity of tubular carbonic anhydrase.

The greatest part of the bicarbonate reabsorption occurs in the proximal convoluted tubule. The secretion of ammonia

and the acidification of the urine take place in the distal convoluted tubule. That portion of bicarbonate which may escape reabsorption in the proximal tubule is reabsorbed in the distal tubule in competition with the fixed anions for the hydrogen ion exchange mechanism. By this means, the plasma bicarbonate can exert some control over the base-sparing mechanisms. When the plasma bicarbonate is low (under approximately 20 mEq. per liter), bicarbonate is completely reabsorbed in the proximal tubules and the other mechanisms are free to utilize all of the distal hydrogen ion exchange. When the plasma bicarbonate is elevated, proximal bicarbonate reabsorption becomes incomplete. The bicarbonate then competes for the hydrogen ions in the distal tubule and thus decreases urine ammonia and titratable acidity.[66]

In the patient with deficient bicarbonate reabsorption, the bicarbonate in the distal tubule at low plasma bicarbonate levels inhibits ammonia formation and the production of titratable acid in the same manner as it does in the normal person with an elevated plasma CO_2.

It is apparent that the impaired bicarbonate reabsorption is the important cause of the acidosis of the Fanconi syndrome. The failure of the ammonia and titratable acidity to prevent acidosis is due to the inhibitory effect of bicarbonate in the distal tubule.

In earlier studies on cystinosis the urinary ammonia excretion was considered to be abnormally high. The increased ammonia in an alkaline urine was regarded as a unique feature of this disease and another indication of the defect in protein metabolism.[86]

This interpretation resulted because the ammonia excretion was compared with the normal (nonacidotic) value and because it was considered that an alkaline urine should be accompanied by a low urinary ammonia content.

The improved understanding of the mechanism of activation and control of renal ammonia production has resolved the confusion arising from the paradoxical urinary ammonia findings in these patients.

Ammonia excretion has been considered to be a passive process, dependent on the hydrogen ion exchange and responding by simple diffusion out of the cell when the lumenal hydrogen ion concentration is high. This mechanism was proposed because of the observations that the urinary ammonia has an almost constant inverse relation to pH during either acidosis or alkalosis [66] and because the inhibition of carbonic anhydrase depresses ammonia output immediately, coincident with the change in pH and despite the presence of systemic acidosis.[98]

However, Pitts [66] has demonstrated that the excretion of ammonia at any given urine pH is higher in an acidotic dog than in a normal dog, showing that some factor other than urine pH must influence ammonia production. The slow response to induced acidosis and the slow disappearance after correction of acidosis also demonstrate a partial independence of urine pH, as does the occurrence in other diseases of increased ammonia with an alkaline urine and systemic acidosis.[99] Rector et al.[100] found that the initially low ammonia output after carbonic anhydrase inhibition rose to levels higher than those of the controls in a few days, even though the urine remained alkaline. The increase in ammonia was correlated with a large increase in renal glutaminase activity. These results indicate that even marked depression of hydrogen ion concentration in the tubular urine does not prevent the ammonia response to acidosis, if enough time elapses for the activity of the ammonia-producing enzymes to increase. They also suggest that the ammonium ion may be transferred intact to the tubular lumen through an ion exchange with sodium or hydrogen, rather than being formed from ammonia which has diffused from the cell.

Whatever the method of transfer from cell to lumen may be, it is clear that the amount of ammonia secreted by the kidney is a resultant of two factors. The first is

the activity of glutaminase (and the other ammonia-forming enzymes [101,102]) in the tubular cells, which determines the capacity of the distal tubule to synthesize ammonia. The second is the hydrogen ion concentration of the urine, which determines how much ammonia can diffuse or be exchanged at any level of enzyme activity.[66]

This mechanism explains the apparently anomalous urinary ammonia findings in patients with the Fanconi syndrome. The acidosis stimulates ammonia production, but the alkaline tubular urine prevents it from rising as high as the acidosis would otherwise demand. The result is a value intermediate between the nonacidotic and the acidotic values in a person with normal kidneys. The ammonia is "relatively high" if judged by the urine pH and "relatively low" if judged by the severity of the acidosis.

The response of the titratable acidity is similar to that of ammonia. The titratable acidity is higher than normal but lower than expected in the presence of acidosis. The titratable acid is increased because of the large increase in the urinary excretion of two important buffers, phosphate and organic acids. The failure of the titratable acidity to rise to the expected level in spite of the large increase in buffer substance is due to the diversion of part of the hydrogen ion exchange mechanism to bicarbonate reabsorption, which allows a large percentage of the buffer to be excreted as the alkaline salt rather than as the acid salt or the acid.

Although the potassium clearance was not elevated at the time the clearance studies were carried out in Case 2, there is little question that excessive urinary excretion was the cause of the hypopotassemia which occurred in both of our patients and which is probably present at sometime in most patients with the Fanconi syndrome. The high clearance and the occurrence of hypopotassemia have both been well documented.[22,31,43,55] The loss of potassium in the urine probably represents a failure of proximal tubular reabsorption, although the secretion of potassium by the distal tubules as a consequence of the inhibited hydrogen ion exchange may contribute, in a manner similar to that which occurs when carbonic anhydrase is inhibited.[103]

In addition to the clinically obvious deficiencies of reabsorption, the proximal tubular insufficiency is also characterized by deficiencies of secretion. This was manifest in Case 2 of this report by a marked lowering of the PAH clearance and the Tm_{PAH}. The same deficiency of PAH excretion was present in the adult patient reported by Sirota and Hamerman,[43] and that patient also had deficient tubular excretion of creatinine and phenol red. The reduced phenolsulfonphthalein (PSP) clearance with normal urea clearance reported by Linder et al.[7] probably represents a similar deficiency in proximal tubular secretory ability.

The secretory insufficiency of the proximal tubule is not important in the pathogenesis of the Fanconi syndrome, but it does demonstrate conclusively the severity and the generalized nature of the tubular hypofunction.

The findings of Sirota and Hamerman[43] are of particular interest because they are in almost complete agreement with those reported here. These observations demonstrate that the abnormal physiology in the childhood and in the adult form of the Fanconi syndrome is apparently identical. Although this similarity would ordinarily be considered self-evident, the apparent difference in the method of inheritance[104] and the fact that cystinosis is limited to the childhood form of the Fanconi syndrome might suggest that the etiology is different. The patient of Sirota and Hamerman had severe reabsorptive defects for glucose, amino acids, phosphate, bicarbonate, and uric acid, in addition to the secretory defects mentioned above.

Our results, and those of Sirota and Hamerman, support the original postulation of Fanconi[82] that the presence of a glomerulotubular imbalance is an important feature

of the syndrome. The contribution of this imbalance to the manifestations of the Fanconi syndrome is evident. Since the amount of material presented for reabsorption depends on the glomerular filtration rate and the plasma level of the substance concerned, a relatively normal glomerular filtration rate is a prerequisite to the overt expression of the tubular dysfunction. The high filtration rate relative to the reabsorptive capacity elevates the ratio of glomerular function to tubular function, and it is the magnitude of this ratio, rather than the severity of the tubular disorder per se, which determines how much of a normally reabsorbed substance will be lost into the urine at any plasma level. If the glomerular filtration rate could be progressively lowered while tubular function and plasma level remained unchanged, a point would be reached at which the amount of the substance filtered would be just equal to the tubular capacity for reabsorption. At this point, the "clearance" of the substance would appear to be normal and the tubular dysfunction would no longer be evident.

Variations in the extent of the imbalance may explain some of the clinical variations that have been noted.[22,35,45,51] The difference in severity from case to case may be due in part to differences in the glomerular filtration rate, in addition to differences in the severity of the tubular disorder.

The mild or absent glycosuria, aminoaciduria, phosphaturia, and acidosis of the chronic form of the Fanconi syndrome as compared with the acute form do not indicate necessarily a fundamental etiological difference in these two forms of this syndrome, as others have implied.[22,45] Nor does it necessarily indicate that improvement in the tubular function has occurred. The difference between the acute phase and the chronic phase of the Fanconi syndrome seems better explained by the decline of glomerular function as the disease progresses. The fall of the glomerular filtration rate decreases the load on the tubules, and the residual loss of glucose, amino acids, phosphate, and bicarbonate after reabsorption is correspondingly decreased. The end-result, of course, is uremia, and in this stage the tubular disease becomes relatively unimportant in comparison with the glomerular insufficiency.

An appreciation of the glomerulotubular imbalance becomes most important when evaluating the response to therapy, especially when considering the implications of the therapeutic response for the etiology and the prognosis. The demonstrations [14,22,42,49] that treatment with vitamin D and base not only corrected the rickets but also decreased the urinary excretion of amino acids, glucose, and ammonia, suggested the possibility that such therapy might be improving tubular function. The "reversibility" of the tubular abnormalities naturally led to a certain amount of optimism regarding the ultimate outcome of these cases.

Our studies confirmed the fall in excretion rates and decrease in the acidosis following massive vitamin D therapy. However, they add nothing to the optimism engendered by the earlier reports. To the contrary, in our patient the response seemed best explained by a decrease in the glomerulotubular imbalance, produced by a decrease in the glomerular filtration rate.

We cannot eliminate the possibility that vitamin D has a direct effect on tubular function. However, we could demonstrate no such effect. Therefore, we would conclude that treatment with vitamin D and alkali improves the patient clinically but probably does not improve his tubular function. The conclusions that other therapeutic agents [36,105] improve tubular function in this disease must also be evaluated in this light, since the natural progression of the disease or an effect of the drug on the glomerular filtration rate could result in an apparent improvement in the blood and urine, as has been reported.

The desire to formulate a unifying theory which would explain why cystinosis and the Fanconi syndrome occur so frequently together has led many investigators to search

for some cause other than renal tubular disease to explain the urinary abnormalities of the Fanconi syndrome. However, from the evidence presented, there would seem to be little reason to doubt the significance of the tubular defect in the pathogenesis of this syndrome. In addition to the urinary abnormalities themselves, most of the symptoms and physical findings can also be explained by the rickets, acidosis, dehydration, and hypopotassemia which are a consequence of the renal dysfunction. Therefore, the Fanconi syndrome, whether accompanied by cystinosis or not, can be considered to be result of dysfunction of the proximal convoluted tubules. The abnormality has been placed in the proximal convolution because it is this segment of the tubule which is responsible for the reabsorption and secretion of all the substances which these patients handle abnormally.

Since the defect is centered in a circumscribed location, and since the reabsorptive and secretory processes are enzymatically controlled, it is evident that either an anatomic abnormality or a defect of the enzyme systems of the proximal convoluted tubules could produce the hypofunction which causes the Fanconi syndrome. Suggestive findings have been presented in favor of each of these possibilities.

Clay et al.[78] found a consistent defect of the proximal tubules in two patients with the Fanconi syndrome, consisting of a narrowing of the first portion of the tubule and shortening of the entire proximal convoluted tubule. They considered these anatomic changes severe enough to explain the existing functional defect. These authors maintain that the consistency and regularity of the tubular defect favor a congenital rather than a toxic basis. However, it seems entirely possible that the same consistency of location could be produced by tubular damage, if the toxic substance which damaged the tubule were specifically localized to the proximal convoluted tubule.

Favoring the hypothesis that an enzymatic abnormality might explain the Fanconi syndrome is the finding of Harrison and Harrison[92] that maleic acid produces in rats all of the urinary changes characteristic of the Fanconi syndrome. Immediately after the intraperitoneal injection of sodium maleate, a marked increase in urinary amino acids, glucose, and phosphate occurs. The glycosuria and phosphaturia are definitely renal in origin, and it is presumed that the amino-aciduria also has a renal basis. Prior studies which led to these incisive experiments had provided evidence that maleic acid decreases the ability of the kidney to acidify the urine.[106]

The tubular abnormality of the Fanconi syndrome is simulated in part by a number of other disorders, both congenital and acquired. The etiologic connection between these disorders of tubular function is rather obscure, but the functional abnormalities are similar enough to suggest that some connection may exist.

Generalized amino-aciduria has been described in a large number of apparently unrelated disorders, both congenital and acquired. The first of these in which amino-aciduria was found is hepatolenticular degeneration (Wilson's disease), a hereditary condition caused by a deficiency of ceruloplasmin, in which an excessive deposition of copper occurs in various tissues.[107] Accompanying the abnormal copper metabolism is a generalized amino-aciduria which occurs in the presence of a normal plasma α-amino nitrogen. The amino-aciduria is remarkably similar to that of the Fanconi syndrome. A quantitative chromatogram[59] of the urine from a patient with Wilson's disease was almost identical to the one obtained in the same laboratory from Patient 2 of this report.[59] Both patients excreted essentially no taurine, increased amounts of threonine, and little combined glycine. Other authors have reported similar findings.[108,109]

The similarity of the amino-aciduria in Wilson's disease to that observed in the Fanconi syndrome suggests that the pathogenesis of the renal disease might be similar in the two conditions. This suggestion is

reinforced by the observations of Cooper et al.,[108] who reported renal glycosuria in three of their six patients with Wilson's disease and deranged calcium and phosphorus metabolism with osteomalacia in one of the six. In addition, Bradley et al.[110] demonstrated a depression of PAH clearance with a normal glomerular filtration rate in two patients with Wilson's disease, suggesting that a glomerulotubular imbalance contributes to the urinary abnormalities of Wilson's disease as well. Bearn et al.,[111] in a more extensive study, found reduced PAH clearance in eight patients with hepatolenticular degeneration. Tm_{PAH} was low in the six patients in whom it was measured, and Tm_G was low in the four patients in whom it was measured. Inulin clearance was normal or moderately reduced in the six cases of relatively short duration but reduced in those with longer-standing disease. All nine had elevated urate clearance; six had elevated amino acid clearance, and six had low serum phosphate and elevated phosphate clearance. Bicarbonate reabsorption was reduced, relative to the serum bicarbonate level, in the four in whom it was measured.

The renal dysfunction of Wilson's disease is generally considered to be due to the toxic effect of the increased tissue copper on the kidneys.[107] The data of Bearn et al.[111] furnish strong support for this belief. The apparent progressive impairment of proximal tubular function and the eventual depression of glomerular filtration suggest that the kidneys are being progressively damaged rather than being affected by a primary hereditary metabolic defect.

Another congenital disorder in which amino-aciduria occurs is galactosemia. In this condition, also, the amino aciduria is generalized and occurs at normal plasma levels.[112] In addition to amino-aciduria, glucosuria [112] and metabolic acidosis with an alkaline urine [113] have been reported in galactosemia. The amino-aciduria of galactosemia decreases or disappears if the galactosemia and galactosuria are eliminated by the feeding of a lactose-free diet. The amino-aciduria does not appear for at least a few days after galactosuria begins [41] and persists for a short time after the galactosuria is stopped.[113] The amino-aciduria, therefore, depends on the presence of galactosemia (or galactosuria), and this dependence indicates that the amino-aciduria is not the result of a congenital defect of the tubule. The delayed onset and disappearance of amino-aciduria demonstrates that the amino-aciduria is due to diminished tubular function rather than to simple competition for reabsorption by galactose. In this disease the toxic substance is presumably galactose-1-phosphate.[113]

A similar phenomenon may be the amino-aciduria which occurs as one of the responses to intoxication with a number of different toxins [114] and in deficiency diseases.[115] Presumably, the amino-aciduria in each of these disorders is due to a renal reabsorptive defect caused by the toxic effect of the substance on the enzyme system(s) of the tubule responsible for amino acid reabsorption. In addition to amino-aciduria, lead poisoning may also be accompanied by renal glycosuria, phosphaturia, hypophosphatemic rickets, and acidosis with an alkaline urine.[114]

The renal abnormalities of the Fanconi syndrome are closely duplicated by the syndrome first described by Lowe et al.[116] and later by Bickel and Thursby-Pelham [41] and Worthen and Good [117] in which congenital cataracts and mental retardation are accompanied by hyperchloremic acidosis, rickets, amino-aciduria, and an alkaline urine with relative failure of the ammonia mechanism to spare fixed base.

The functional disturbance of the proximal tubule in this syndrome is the same as that of the Fanconi syndrome, including the presence of a glomerulotubular imbalance and tubular insufficiency for both secretion and reabsorption.[117] However, the tubular dysfunction is generally less severe than in the Fanconi syndrome.

In addition to these generalized disorders of tubular function, hereditary diseases with

disturbance of only a single function may simulate a portion of the Fanconi syndrome. In each of these isolated disorders—renal glycosuria, cystinuria, renal tubular acidosis, and vitamin D-resistant rickets—the abnormality is presumed to be due to a primary absence or deficiency of an essential enzyme system in the proximal tubules.

The occurrence of each of these abnormalities as an inherited defect suggests the possibility that the Fanconi syndrome might represent a hereditary defect of the tubules encompassing all of these abnormalities. However, since the Fanconi syndrome is duplicated much more closely by those hereditary disorders in which the tubular dysfunction appears to be secondary to the toxic action of some metabolite, it is far more probable that the Fanconi syndrome itself is secondary to tubular damage.

In patients with cystinosis, this probability seems overwhelming. The known nephrotoxicity of cystine,[118-121] with the early predelection for the proximal convolutions[118] and later diffuse renal damage; the nearly exact reproduction of the Fanconi syndrome by maleate and lead poisoning, and the progressive nature of the renal disease leave little doubt that cystine in some as yet obscure manner produces the tubular abnormality which results in the Fanconi syndrome.

In patients without cystinosis the evidence for a toxic process is not so striking. However, the fact that the Fanconi syndrome without cystinosis appears identical to the syndrome which accompanies cystinosis, including the progressive course to renal failure, suggests that an unrecognized toxin exists in these patients which is capable of simulating the action of cystine. The frequent occurrence of cirrhosis in these patients[53,122] indicates that a toxin may be present which is capable of damaging the liver as well as the renal tubules. In addition, the Fanconi syndrome has been reported in three cases of multiple myeloma.[43, 52,54] In one of these patients,[54] crystal-like inclusions (presumably protein) similar to those observed within the plasma cells were found in the cells of the cortical tubules. This evidence suggests that the abnormal protein, or some other metabolite has produced the reabsorptive defects in this patient and adds further support to the hypothesis that other toxins may produce the renal tubular damage.

The etiology of cystinosis itself is still an enigma. Various theories have been presented to explain the deposition of cystine crystals in reticuloendothelial tissues, but none has been completely satisfactory. One obstacle is that most hypotheses have been formulated to explain not only the cystine deposits but also the other clinical and urinary abnormalities. Accepting the renal defect as the basis for the clinical and laboratory manifestations should permit a more incisive approach to an understanding of the cystinosis.

The original theory that the reticuloendothelial cells accumulate cystine by phagocytosis has been replaced by the theory that the metabolic abnormality responsible for cystine accumulation exists in the reticuloendothelial cells themselves and that cystine accumulates where it is being produced.[22] Although some evidence favors this possibility, none is direct. It remains to be determined whether the reticuloendothelial cells alone are involved or whether the same anomaly exists in other cells, with accumulation of cystine in the reticuloendothelial cells as a compensation for abnormal metabolism in other cells of the body.

Bickel's contention that the cystinosis results from a defect in protein metabolism can be acceptable only if this defect is considered to be confined to the reticuloendothelial system. A defect of protein anabolism involving all the body cells is virtually eliminated by the observation that plasma amino acid and protein levels are regularly normal and by the fact that a normal turnover rate of plasma proteins has been demonstrated in cystinosis.[55] However, it is possible that defective protein synthesis might exist in one system of cells

without producing detectable alteration of the total protein metabolism.

The proponents of this theory have presented evidence that the concentrations of tyrosine [36] and arginine [22] are also increased in the areas of cystine storage, and they suggest that these amino acids reflect a generalized defect in amino acid utilization. However, this evidence is equivocal, because these amino acids were determined histochemically, and the reaction of free amino acids would be difficult to differentiate from the reactions due to proteins of these tissues. Schiff [47] and Cogan et al.,[50] using chromatography, could find no free amino acid other than cystine in the conjunctiva. This evidence is more definitive, because the method is more reliable and because the contamination from protein amino acids is eliminated. In addition, Barr and Barr [123] have demonstrated conclusively that tyrosine crystals are not present and that the atypical crystals which were thought to be tyrosine are variants of the more typical cystine crystals. From these observations, it must be concluded that cystine is the only amino acid for which proof of abnormal accumulation can be considered established. Therefore, whether the defect is localized to the reticuloendothelial cell or not, it appears reasonable to conclude that the abnormality of cystinosis is produced by a specific defect in the metabolism of cystine rather than by some basic defect in protein metabolism.

Cystine accumulation could conceivably occur from a block anywhere in the metabolism of the sulfur-containing amino acids. However, cystine is not directly on the main metabolic pathway of the sulfur amino acids but enters by being converted to cysteine, and so a defective reduction of cystine to cysteine is the most probable site of the abnormality. A defect in this step would be the most difficult to circumvent by an alternative pathway.

An enzyme which catalyzes the reduction of cystine to cysteine by reduced diphosphopyridine nucleotide (DPNH) has been demonstrated in both plant and animal tissues.[124] The enzyme has been named cystine reductase, and it is apparently specific, both for cystine and for the co-enzyme.

Since several other inborn errors of metabolism have been found to be due to a specific enzyme deficiency,[125] it is attractive to postulate that a deficiency in cystine reductase is responsible for cystinosis. However, the same effect might be produced by a decrease in the rate of DPNH formation or by a relative decrease in the nonenzymatic reducing substances which may contribute to the reduction of cystine to cysteine.[124]

Consideration of the mechanism by which cystine might exert its effect on the kidney has been centered around the relation of cystine to methionine and the action of cystine in increasing the severity of the lesions produced by choline deficiency.[105] However, the studies on maleate and lead toxicity and the demonstration of the renal abnormalities of Wilson's disease suggest an alternative mechanism which fits the observed facts more satisfactorily. Maleic acid is an unsaturated dibasic acid which forms addition compounds with sulfhydryl groups.[126] It, therefore, inhibits enzymes or co-enzymes which require free SH groups for activity.[127] This action is duplicated in vitro by many oxidizing agents and heavy metals, among them cystine, copper, and lead.[128] Aside from their action on sulfhydryl groups, cystine, maleic acid, and the two metals are dissimilar. Therefore, the fact that the in vivo occurrence of each substance is associated with essentially the same disorder of renal function suggests to us that these agents act by inhibiting SH-dependent enzymes of the proximal convoluted tubules.

Since a large number of enzymes and coenzymes require free SH groups for activity, the inhibition of these groups would be expected to produce multiple defects such as those which characterize the Fanconi syndrome. The inhibition of SH enzymes of various energy cycles might reduce the energy available to the tubule and thus produce a generalized proximal tubular in-

competence, or, alternatively, each of the affected functions might have an SH-dependent step and, therefore, be directly inhibited.

The production of these proximal tubular defects is not a universal property of sulfhydryl inhibitors. The reason for the characteristic action of these four agents could be that they are concentrated in the area of the proximal convoluted tubule to a greater extent than are some other inhibitors. This concept is supported by the observation that a major site of damage in both cystinosis and lead poisoning [114] is the proximal convoluted tubule. The failure of mercury (a potent sulfhydryl blocking agent) to produce a pathologic physiology similar to the Fanconi syndrome may be explained by the fact that mercury exerts its action on SH groups beyond the proximal convolution, chiefly on the straight segment of the proximal tubule, the loops of Henle, and the collecting ducts.[129]

Since the Fanconi syndrome in patients without cystinosis is so strikingly similar to the syndrome which accompanies cystinosis, it may be that the Fanconi syndrome occurring without cystinosis is due to an inhibition of sulfhydryl-dependent enzymes by a different oxidizing agent, which has an action similar to cystine. However, since the tubular effects of cystine may be manifestations only of a reduction in available energy, it may be that inhibitors acting by mechanisms other than oxidation could produce the same functional result. The similarity of the renal effects of galactosemia supports this possibility, since galactose-1-phosphate presumably exerts its toxic action by inhibiting the phosphoglucomutase reaction, and the tubular abnormalities are probably due to the deficiency of an energy source required by the proximal tubule.

Since progress toward total renal insufficiency occurs in the patients with the Fanconi syndrome whether or not cystinosis is present, it seems probable that the pathologic changes in the tubule and the later involvement of the glomerulus are consequences of the altered enzyme activities rather than of some other toxic effect of cystine itself.

If sulfhydryl inhibition is indeed the basis for the tubular abnormality, the possibility of developing an effective therapy becomes more promising. Treatment with either stable sulfhydryl compounds or less-specific reducing agents may remove the inhibition of the enzymatically active sulfhydryl groups and restore the tubular function to normal. If such an agent would be used early in the course of cystinosis, it might also prevent structural alteration of the tubules as well as the seemingly inevitable progression to renal insufficiency with the consequent uremia. It is conceivable that such a reducing agent might also increase the reduction of cystine to cysteine and thus eliminate the cystine storage as well as the tubular dysfunction. Although this possible approach has not been thoroughly tested and may seem somewhat overoptimistic, clinical evidence is already available that provokes consideration. Dimson [33] administered α-tocopherol to a patient with cystinosis in the hope that it might prevent the oxidation of cysteine to cystine. After six months of treatment with 100 mg. per day, the cystine deposits in the cornea seemed to be significantly reduced. Renal function also improved, even though renal failure was far-advanced when treatment was started.

The effect of vitamin E on the tubular function of this case cannot be evaluated, but the effect on the cystine storage seems definite. Since a relatively mild reducing agent is at least partially effective, it seems probable that more potent reducing agents may do even more to reverse the cystine storage and restore tubular function toward normal.

Although the mechanisms suggested above are based chiefly on theoretical considerations, the possibility that a therapy might be developed which could ameliorate the underlying defect demands further investigation along these lines.

Summary

Two typical cases of the Fanconi syndrome with cystinosis are presented. These cases demonstrate all of the diagnostic features of this condition: vitamin D-resistant hypophosphatemic rickets, hypercloremic acidosis with alkaline urine, renal glycosuria, renal amino-aciduria, renal phosphaturia, and cystine crystals in the cornea and bone marrow.

The difficulties in management are illustrated by both cases, primarily, the ever-present danger of hypopotassemia and the difficulty in regulating the dose of vitamin D.

The second case illustrates the clinical improvement which follows healing of the rickets.

Evidence is presented to support the hypothesis that the clinical picture is the result of a defect of the proximal convoluted tubule.

The contribution of the glomerulotubular imbalance to the syndrome is demonstrated by Case 2. A recognition of the modifications which occur with alteration of the glomerular filtration rate will help avoid the error of making specious assumptions, particularly with regard to therapy, based only on changes in the urine.

The resemblance of the renal defect to that of other hereditary disorders, especially Wilson's disease and Lowe's syndrome, is illustrated. The significance of this resemblance regarding the etiology is discussed.

Theories regarding the etiology of the tubular abnormality and cystinosis are reviewed. The concept most attractive to us in explaining both cystinosis and renal tubular disease is presented.

University of Minnesota, 402 Heart Hospital (14).

REFERENCES

1. Fanconi, G.: Weitere Beitraege zur Cystinkrankheit (der Amindiabetes), Helvet. paediat. acta 1:183, 1946.

2. Stowers, I., and Dent, C. E.: Studies on the Mechanism of the Fanconi Syndrome, Quart. J. Med. 16:275, 1947.

3. Hottinger, A.: Zur Cystindiathese, Ann. paediat. 169:272, 1947.

4. Maschas, H.; Lamotte, M.; Lamotte-Barrillon, S., and Barbier, P.: Un Cas de cystinose revilée par une lithuse urinaire, Bull. et mém. Soc. méd. hôp. Paris 64:491, 1948.

5. Ullrich, O.: Zur Klinik und Erbbiologie der Cystin-diathese als uebergeordneter Stoerung bei renalem Zwergwuchs and renaler Rachitis, Ztschr. Kinderh. 66:154, 1949.

6. D'Avignon, M., and Vahlquist, B.: Un Cas de cystinose: Syndrome de Fanconi-de Toni-Debre, Arch. franç. pédiat. 6:351, 1949.

7. Linder, G. C.; Bull, G. M., and Grayce I.: Hypophosphataemic Glycosuric Rickets (Fanconi Syndrome), Clin. Proc. 8:1, 1949.

8. Fanconi, G., and Bickel, H.: Der chronische Aminoacidurie bei der Glycogenose und der Cystinkrankheit, Helvet. paediat. acta 4:359, 1949.

9. Hingston, J.: An Unusual Case of Rickets (Fanconi Syndrome), Brit. M. J. 2:1393, 1949.

10. Melle, B. G. V. B., and Barnes, H. D.: A Case of Fanconi-de Toni Syndrome (Cystine Disease), S. African M. J. 24:269, 1950.

11. Barnes, H. D.: Partition Chromatography of Urinary Amino Acids, S. African M. J. 24:272, 1950.

12. Bakx, C. J. A.: Renal Rickets, Renal Diabetes and Cystine Metabolism (Syndrome of de Toni-Fanconi-Debre), Nederl. tijdschr. geneesk. 94:2326, 1950.

13. Douglas, A. A.: A Case of the Syndrome of Fanconi, Tr. Ophth. Soc. U. Kingdom 70:98, 1950.

14. Stevenson, F. H.: Fanconi-Type Resistant Rickets, Proc. Roy. Soc. Med. 43:907, 1950.

15. Dent, C. E., and Harris, H.: Genetics of Cystinuria, Ann. Eugenics 16:60, 1951.

16. King, F. P., and Lockridge, E. P.: Cystinosis (Cystine Storage Disease): Report of a Case with Chemical Isolation and Quantitative Determination of Cystine in Lymph Nodes, Spleen, and Liver, A. M. A. Am. J. Dis. Child. 82:446, 1951.

17. Monod, C.: Un Cas de Cystinose, Helvet. paediat. acta 6:534, 1951.

18. Linneweh, F.: Beitrag zur Frage der chronischen Aminoacidurie: Vergleichende Untersuchungen über Cystinurie und Cystinspeicherkrankheit, Klin. Wchnschr. 29:633, 1951.

19. Drablos, A.: The de Toni-Fanconi Syndrome with Cystinosis, Acta paediat. 40:438, 1951.

20. Muller, H. K.: Über die Bedeutung von Augenveraenderungen für die Diagnose der Zystinkrankheit im Kindesalter, Klin. Monatsbl. Augenh. 119:205, 1951.

21. Braendstrup, P.: Infantile Cystinosis with Cystine Crystals in Cornea and Conjunctiva, Acta ophth. 30:365, 1952.

22. Bickel, H.; Baar, H. S.; Astley, R.; Douglas, A. A.; Harris, H.; Hickmans, E. M.; Smallwood,

W. C.; Smellie, J. M., and Teall, C. G.: Cystine Storage Disease with Aminoaciduria and Dwarfism (Lignac-Fanconi Disease), Acta paediat. 42 (Supp. 90) :7-237, 1952.

23. Philpott, M. G.; Harvey, C. C., and Finch, E.: Detailed Clinical and Biochemical Report of 2 Brothers Suffering from Lignac-Fanconi Disease, Acta paediat. 42 (Supp. 90) :114-136, 1952.

24. Guild, H. G.; Walsh, F. B., and Hoover, R. E.: Ocular Cystinosis, Am. J. Ophth. 35:1241, 1952.

25. Kennedy, J. A.: Cystinosis with Crystal Deposits in the Cornea and Conjunctiva, Am. J. Ophth. 35:1596, 1952.

26. Brown, R. J. K.: A Clinical-Pathological Study of Cystinosis in 2 Siblings, Arch. Dis. Childhood 27:428, 1952.

27. Weyers, H.: Neue Befunde zur Diagnose und Klinik der chronischen Aminoacidurie und Cystinspeicherung, Acta paediat. Uppsala 41:334, 1952.

28. Williamson, D. A. J.: Cystinosis, Arch. Dis. Childhood 27:356, 1952.

29. Boehncke, H.; Weyers, H., and Tepe, H. J.: Beobachtungen bei Cystinspeicherkrankheit, Ztschr. Kinderh. 72:1, 1952.

30. Harper, H. A.; Grossman, M.; Henderson, P., and Steinbach, H.: Renal Amino-Aciduria: Report of 2 Cases, with Studies of Amino Acid Excretion Patterns, A. M. A. Am. J. Dis. Child. 84:327, 1952.

31. Milne, M. D.; Stanbury, S. W., and Thomson, A. E.: Observations on the Fanconi Syndrome and Renal Hyperchloraemic Acidosis in the Adult, Quart. J. Med. 21:61, 1952.

32. Anderson, I. A.; Miller, A., and Kenney, A. P.: Osteomalacia and Renal Glycosuria in Adults: Metabolic Investigations of Case with Particular Reference to Its Relation to Fanconi Syndrome and to Treatment, Quart. J. Med. 21:33, 1952.

33. Dimson, S. B.: The Fanconi Syndrome in 2 Siblings, Proc. Royal Soc. Med. 45:454, 1952.

34. Jackson, H. F., and Clark, B. E.: Cystinosis: Report of 2 Cases with Postmortem Examination, A. M. A. Am. J. Dis. Child. 85:531, 1953.

35. Weber, H.: Beitrag zur Frage der Nierenfunktionsstoerung bei Cystinosis, Helvet. paediat. acta 8:348, 1953.

36. Freudenberg, E.: Weitere Beobachtungen zur Frage der Cystinosis, Ann. paediat. 182:85, 1954.

37. Caussade, L.; Neiman, N., and Pierson, M.: Considérations sur la cystinose, Presse méd. 62: 646, 1954.

38. Kyle, L. H.; Meroney, W. H., and Freeman, M. E.: Study of the Mechanism of Bone Disease in Hypophosphatemic Glycosuric Osteomalacia, J. Clin. Endocrinol. 14:365, 1954.

39. Myerson, R. M., and Pastor, B. H.: The Fanconi Syndrome and Its Clinical Variants, Am. J. M. Sc. 228:378, 1954.

40. Burki, E.: Ein Weiterer Fall von Cystinosis mit Hornhautveränderungen, Ophthalmologica 127:309, 1954.

41. Bickel, H., and Thursby-Pelham, D. C.: Hyper-Aminoaciduria in Lignac-Fanconi Disease, Galactosaemia and in an Obscure Syndrome, Arch. Dis. Childhood 29:224, 1954.

42. Salassa, R. M.; Power, M. H.; Ulrich, J. A., and Hayles, A. B.: Observations on the Metabolic Effects of Vitamin D in Fanconi's Syndrome, Proc. Staff Meet. Mayo Clin. 29:214, 1954.

43. Sirota, J. H., and Hamerman, D.: Renal Function Studies in an Adult Subject with the Fanconi Syndrome, Am. J. Med. 16:139, 1954.

44. Perry, J. W.; Moore, A. E., and MacDonald, W. B.: The Diagnosis of Aminoaciduria in Childhood: Cystine Storage Disease and Cystine-Lysinuria, M. J. Australia 2:812, 1954.

45. Israels, S., and Suderman, H. J.: Cystinosis, J. Pediat. 47:73, 1955.

46. Latham, W.; Baker, K., and Bradley, S. E.: Urinary Amino Acid Excretion in Renal Disease, with Observations on the Fanconi Syndrome, Am. J. Med. 18:249, 1955.

47. Schiff, F. S.: Cystine Deposits of Cornea and Conjunctiva, A. M. A. Arch. Ophth. 53:434, 1955.

48. Gatzimos, C. D.; Schulz, D. M., and Newnum, R. L.: Cystinosis (Lignac-Fanconi Disease), Am. J. Path. 31:791, 1955.

49. Parker, W. S.; Prader, A., and Fanconi, G.: Further Observations on Cystine Storage Disease, Pediatrics 16:228, 1955.

50. Cogan, D. G.; Kuwabara, T.; Kinoshita, J.; Sudarsky, D., and Ring, H.: Ocular Manifestations of Systemic Cystinosis, A. M. A. Arch. Ophth. 55:36, 1956.

51. Hooft, C.; Delbeke, M. J., and Herpol, J.: Cystinose chronique associee à une hypothyroidie probable, Ann. paediat. 187:81, 1956.

52. Dragsted, P. J., and Hjorth, N.: The Association of the Fanconi Syndrome with Malignant Disease, Danish M. Bull. 3:177, 1956.

53. Baber, M. D.: A Case of Congenital Cirrhosis of the Liver with Renal Tubular Defects Akin to the Fanconi Syndrome, Arch. Dis. Childhood 31:335, 1956.

54. Engle, R. L., and Wallis, L. D.: Multiple Myeloma and the Adult Fanconi Syndrome, Am. J. Med. 22:5, 1957.

55. Kretchmer, N.: Clinical Conference: Cystinosis, Pediatrics 19:962, 1957.

56. McCune, D. J.; Mason, H. H., and Clarke, H. T.: Intractable Hypophosphatemic Rickets with Renal Glycosuria and Acidosis (the Fanconi Syndrome): Report of a Case in Which Increased

Urinary Organic Acids Were Detected and Identified, with a Review of the Literature, Am. J. Dis. Child. 65:81, 1943.

57. Van Slyke, D. D.; MacFayden, D. A., and Hamilton, P. B.: The Gasometric Determination of Amino Acids in Urine by the Ninhydrin-Carbon Dioxide Method, J. Biol. Chem. 150:251, 1943.

58. Childs, B.: Urinary Excretion of Free Alpha-Amino Acid Nitrogen by Normal Infants and Children, Proc. Soc. Exper. Biol. & Med. 81:225, 1952.

59. Frame, E. G., and Rausch, V. L.: Chromatographic Studies of Urinary Amino Acids, Bull. Univ. Minnesota Hosp. 23:532, 1952.

60. Thompson, R. C., and Abdulnabi, M.: A Study of the Urinary Excretion of Alpha-Amino Nitrogen and Lysine by Humans, J. Biol. Chem. 185:625, 1950.

61. Hamilton, P. B., and Van Slyke, D. D.: The Gasometric Determination of Free Amino Acids in Blood Filtrates by the Ninhydrin-Carbon Dioxide Method, J. Biol. Chem. 150:231, 1943.

62. Dent, C. E.: Study of Amino Acids with Chromatography, Biochem. J. 43:169, 1948.

63. Dent, C. E.: Amino Aciduria in the Fanconi Syndrome, Biochem. J. 41:240, 1947.

64. Stein, W. H., and Moore, S.: Chromatography of Amino Acids on Starch Columns: Separation of Phenylalanine, Leucine, Isoleucine, Methionine, Tyrosine, and Valine, J. Biol. Chem. 176:337, 1948.

65. Van Slyke, D. D., and Palmer, W. W.: Studies of Acidosis: XVI. The Titration of Organic Acids in Urine, J. Biol. Chem. 41:567, 1920.

66. Pitts, R. F.: Acid-Base Regulation by the Kidneys, Am. J. Med. 9:356, 1950.

67. Talbot, N. B.; Sobel, E. H.; McArthur, J. W., and Crawford, J. D.: Functional Endocrinology from Birth through Adolescence, Cambridge, Mass., Harvard University Press, 1952.

68. Bojesen, E.: A Method for Determination of Inulin in Plasma and Urine, Acta med. Scandinav., Supp. 266, p. 275, 1952.

69. Miller, Z., and Miller, B. F.: Specific Determination of Serum Creatinine, Proc. Soc. Exper. Biol. & Med. 78:471, 1951.

70. Smith, H. W.; Finkelstein, N.; Aliminosa, L.; Crawford, B., and Graber, M.: Renal Clearances of Substituted Hippuric Acid Derivatives and Other Aromatic Acids in Dog and Man, J. Clin. Invest. 24:388, 1945.

71. Nelson, N.: Photometric Adaption of the Somogyi Method for the Determination of Glucose, J. Biol. Chem. 153:375, 1944.

72. Fiske, C. H., and Subbarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. 66:375, 1925.

73. Barnett, H. L., and Vesterdal, J.: The Physiologic and Clinical Significance of Immaturity of Kidney Function in Young Infants, J. Pediat. 42:99, 1953.

74. Smith, H. W.: The Kidney: Structure and Function in Health and Disease, New York, Oxford University Press, 1951.

75. McCrory, W. W.; Forman, C. W.; McNamara, H., and Barnett, H. L.: Renal Excretion of Inorganic Phosphate in Newborn Infants, J. Clin. Invest. 31:357, 1952.

76. Pitts, R. F.; Ayer, J. L., and Schiese, W. A.: The Renal Regulation of Acid-Base Balance in Man: III. The Reabsorption and Excretion of Bicarbonate, J. Clin. Invest. 28:35, 1949.

77. Shohl, A. T.: Mineral Metabolism, New York, The Reinhold Publishing Corporation, 1939.

78. Clay, R. D.; Darmady, E. M., and Hawkins, M.: The Nature of the Renal Lesion in the Fanconi Syndrome, J. Path. & Bact. 65:551, 1953.

79. Oliver, J.: An Essay Toward a Dynamic Morphology of the Mammalian Nephron, Am. J. Med. 9:88, 1950.

80. De Toni, G.: Remarks on the Relations Between Renal Rickets (Renal Dwarfism) and Renal Diabetes, Acta paediat., Uppsala 16:479, 1933.

81. Debre, R.; Marie, J.; Cleret, F., and Messimy, R.: Rachitisme tardif coexistant avec une nephrite chronique et une glycosurie, Arch. méd. enf. 37:597, 1934.

82. Fanconi, G.: Der Fruhinfantile nephrotisch-glykosurische Zwergwuchs mit hypophosphatämischer Rachitis, Jahrbuch für Kinderheilkunde 147:299, 1936.

83. Lignac, G. O. E.: Über Störung des Cystinstoffwechsels bei Kindern, Deutsches Arch. klin. Med. 145:139, 1924.

84. Russell, D. S., and Barrie, H. J.: Storage of Cystine in Reticulo-Endothelial System and Its Association with Chronic Nephritis and Renal Rickets, Lancet 2:899, 1936.

85. De Toni, G.: Renal Rickets with Phospho-Gluco-Amino Renal Diabetes (De Toni-Debre-Fanconi Syndrome), Ann. paediat. 187:42, 1956.

86. Rapaport, M.: Inborn Errors of Metabolism: Cystinuria, in Nelson, W. E. Textbook of Pediatrics, Ed. 5, Philadelphia, W. B. Saunders Company, 1950, pp. 288-291.

87. Freudenberg, E.: Cystinosis, Cystine Disease (Lignac's Disease) in Children, in Levine, S. Z., et al.: Advances Pediat. 4:265, 1949.

88. Schreir, K.: Some Peculiarities of Amino Acid Metabolism in Infancy and Early Childhood, J. Pediat. 46:86, 1955.

89. Dent, C. E.: Rickets and Osteomalacia from Renal Tubular Defects, J. Bone & Joint Surg. 34-B:266, 1952.

90. Jackson, W. P. U., and Linder, G. C.: Innate Functional Defects of the Renal Tubules, with Particular Reference to the Fanconi Syndrome, Quart. J. Med. 22:133, 1953.

91. Fanconi, G.: Tubular Insufficiency and Renal Dwarfism, Arch. Dis. Childhood 29:1, 1954.

92. Harrison, H. E., and Harrison, H. C.: Experimental Production of Renal Glycosuria, Phosphaturia and Aminoaciduria by Injection of Maleic Acid, Science 120:606, 1954.

93. Albright, F., and Reifenstein, E. C.: The Parathyroid Gland and Metabolic Bone Disease: Selected Studies, Baltimore, Williams & Wilkins Company, 1948.

94. Schwab, L., and Lotspeich, W. C.: Renal Tubular Reabsorption of Acetoacetate in the Dog, Am. J. Physiol. 176:195, 1954.

95. Vischer, F. E.: Renal Clearance of B-Hydroxybutyric Acid in a Dog, Proc. Soc. Exper. Biol. & Med. 60:269, 1945.

96. Babson, S. G.: Renal Glycosuria, J. Pediat. 17:781, 1940.

97. Somogyi, M.: Changes in Ketonemia and Ketonuria During Hypoglycemia, Proc. Soc. Exper. Biol. & Med. 45:640, 1940.

98. Gilman, A., and Brazeau, P.: The Role of the Kidney in the Regulation of Acid-Base Metabolism, Am. J. Med. 15:765, 1953.

99. De Oliveira, H.: Excretion of Ammonia in Cases of Acute Tubular Necrosis with Acidosis and Alkaline Urine, Metabolism 2:36, 1953.

100. Rector, F. C.; Seldin, D. W.; Roberts, A. D., Jr., and Copenhaver, J. H.: Relation of Ammonia Excretion to Urine pH, Am. J. Physiol. 179:353, 1954.

101. Lotspeich, W. D., and Pitts, R. F.: The Role of Amino Acids in the Renal Tubular Secretion of Ammonia, J. Biol. Chem. 168:611, 1947.

102. Kamin, H., and Handler, P.: The Metabolism of Parenterally Administered Amino Acids: III. Ammonia Formation, J. Biol. Chem. 193:873, 1951.

103. Berliner, R. W.; Kennedy, T. J., Jr., and Orloff, J.: Relationship Between Acidification of the Urine and Potassium Metabolism: Effect of Carbonic Anhydrase Inhibition on Potassium Excretion, Am. J. Med. 11:274, 1951.

104. Dent, C. E., and Rose, G. A.: Amino Acid Metabolism in Cystinuria, Quart. J. Med. 20:205, 1951.

105. Van Creveld, S., and Grunbaum, H.: Renal Rickets and Cystinuria, Acta paediat. scandinav. 29:183, 1942.

106. Berliner, R. W.; Kennedy, T. V., and Hilton, J. G.: The Effect of Maleic Acid on Renal Function, Proc. Soc. Exper. Biol. & Med. 75:791, 1950.

107. Cartwright, G. E.; Hodges, R. E.; Gubler, C.J.; Mohoney, J. P.; Daum, K.; Wintrobe, M. M., and Bean, W. B.: Studies on Copper Metabolism: XIII. Hepatolenticular Degeneration, J. Clin. Invest. 33:1487, 1954.

108. Cooper, A. M.; Eckhardt, R. D.; Faloon, W. W., and Davidson, C. S.: Aminoaciduria in Wilson's Disease, J. Clin. Invest. 29:265, 1950.

109. Stein, W. H.; Bearn, A. G., and Moore, S.: The Amino Acid Content of the Blood and Urine in Wilson's Disease, J. Clin. Invest. 33:410, 1954.

110. Bradley, S. E.; Bradley, G. P.; Tyson, C. J.; Curry, J. J., and Blake, W. D.: Renal Function in Renal Diseases, Am. J. Med. 9:766, 1950.

111. Bearn, A. G.; Yü, T. F., and Gutman, A. B.: Renal Function in Wilson's Disease, J. Clin. Invest. 36:1107, 1957.

112. Darling, S. V., and Mortensen, O.: Aminoaciduria in Galactosaemia, Acta paediat. 43:337, 1954.

113. Holzel, A.; Komrower, G. M., and Schwarz, V.: Galactosemia, Am. J. Med. 22:703, 1957.

114. Chisholm, J. J., Jr.; Harrison, H. C.; Eberlein, W. R., and Harrison, H. E.: Amino-Aciduria, Hypophosphatemia, and Rickets in Lead Poisoning: Study of a Case, A. M. A. Am. J. Dis. Child. 89:159, 1955.

115. Jonxis, J. H. P., and Huisman, T. H. J.: Amino Aciduria and Ascorbic Acid Deficiency, Pediatrics 14:238, 1954.

116. Lowe, C. U.; Terrey, M., and MacLachlan, E. A.: Organic-Aciduria, Decreased Renal Ammonia Production, Hydrophthalmos, and Mental Retardation: A Clinical Entity, A. M. A. Am. J. Dis. Child. 83:164, 1952.

117. Worthen, H., and Good, R. A.: Concept of Renal Tubular Insufficiency with Description of 3 Typical Cases, in Essays on Pediatrics, edited by R. A. Good and E. S. Platou, Minneapolis, Lancet Publications, Inc., 1955, pp. 305-311.

118. Newburgh, L. H., and Marsh, P. L.: Renal Injuries by Amino-Acids, Arch. Int. Med. 36:682, 1925.

119. Lewis, H. B.: The Metabolism of Sulfur: IX. The Effects of Repeated Administration of Small Amounts of Cystine, J. Biol. Chem. 65:187, 1925.

120. Curtis, A. C., and Neubergh, L. H.: The Nephrotoxic Action of Ingested Cystine, J. Clin. Invest. 2:611, 1926.

121. Cox, G. J.; Smythe, C. V., and Fishback, C. F.: The Nephro-Pathogenic Action of Cystine, J. Biol. Chem. 82:95, 1929.

122. Cowie, V.: Hair Colour in the Infantile Fanconi Syndrome, Ann. Human Genetics 21:170, 1956.

123. Barr, H. S., and Barr, S.: The Nature of the Crystalline Material in Tissues of Lingnac-Fanconi's Disease, Acta paediat. 45:551, 1956.

124. Romano, A. H., and Nickerson, W. J.: Cystine Reductase of Pea Seeds and Yeasts, J. Biol. Chem. 208:409, 1954.

125. Garrod, A. E.: Inborn Errors of Metabolism, Ed. 2, London, H. Froude, Hodder and Stoughton, 1923.

126. Morgan, E. J., and Friedmann, E.: Interaction of Maleic Acid with Thiol Compounds, Biochem. J. 32:733, 1938.

127. Morgan, E. J., and Friedmann, E.: Maleic Acid as Inhibitor of Enzyme Reactions Induced by SH Compounds, Biochem. J. 32:862, 1938.

128. Hopkins, F. G.; Morgan, E. J., and Lutwak-Mann: The Influence of Thiol Groups in the Activity of Dehydrogenases: Part II. Biochem. J. 32:1829, 1938.

129. Farah, A.; Cafruny, E. J., and Di Stefano, H. S.: Histochemical Studies on the Site of Action of Mercurial Diuretics, J. Histochem. & Cytochem. 3:271, 1955.

Abstracts from Current Literature

American Heart Journal, St. Louis

Abstracted by Edward C. Matthews, M.D.

55, No. 1 (Jan.) 1958

Acetyl Strophanthidin Used as a Measure to Evaluate the Status of Digitalization. Dietegen von Capeller and Thomas N. Stern.—p. 8.

AVr—An Index of Right Ventricular Preponderance: Correlation of QRS Patterns in AVr and the Right Precordial Leads with the Ventricular Workload Ratio. Richard H. Wasserburger and John H. Brown.—p. 33.

* Mumps Pericarditis: Review of the Literature and Report of a Case. Morris Kleinfeld, Saul Milles, and Martin Lidsky.—p. 153.

Mumps Pericarditis: Review of the Literature and Report of a Case.—It is estimated that the incidence of myocardial involvement in patients with mumps is about 5%. While mumps myocarditis is usually manifested by electrocardiographic changes in the absence of symptoms relative to the cardiovascular system, deaths have been ascribed to the myocardial involvement. Isolated cases of mumps pericarditis have been reported in the past.

The case reported is of a 16-year-old white youth admitted to the hospital with a seven-day history of respiratory distress, characterized by a heaviness in the chest associated with restricted breathing, and a two-day history of substernal chest pain aggravated by deep inspiration and recumbency. On admission, there were no physical findings to suggest mumps but the electrocardiogram was consistent with acute pericarditis, suggesting viral pericarditis as the most likely diagnosis. On the third hospital day the chest pain disappeared but bilateral swelling and tenderness in the parotid and submaxillary regions was noted and the parotid duct orifices were reddened and patulous. Five days thereafter spinal fluid showed a lymphocytic pleocytosis without other abnormalities, and seven days thereafter testicular pain and swelling developed. A rise in the mumps complement-fixation titer was demonstrated. The electrocardiogram reported 22 days after the date of admission still reflected changes in the course of the pericarditis.

This case is unusual in that the commoner clinical manifestations of mumps were ushered in by symptoms and electrocardiographic evidence of pericarditis.

American Journal of Medicine

Abstracted by Hugo Dunlap Smith, M.D.

22, No. 6 (June) 1957

* Fungus Infections Associated with Antibiotic and Steroid Therapy. Richard M. Torack.—p. 872.

The Significance of Bronchiectasis Associated with Pulmonary Tuberculosis. John K. Curtis.—p. 894.

Accuracy of the Confirmatory Diagnosis of Tuberculosis. Albert R. Allen, Robert W. J. Harmon, Louis J. Klacsan, and Kenneth M. Stewart Jr.—p. 904.

Brucellosis in Egypt: A Review of Experience with 228 Patients. W. C. E. Pfischner Jr., K. G. Ishak, E. M. Neptune Jr., S. M. Fox III, Zoheir Farid, and Gamal Nor El Din.—p. 915.

Clinical Evaluation of Enzymatic Therapy in Diseases of the Chest. Seymour M. Farber, Roger H. L. Wilson, and Orville F. Grimes.—p. 930.

23, No. 1 (July) 1957

The Concept of Relative Bone Marrow Failure (editorial). Carl V. Moore.—p. 1.

* Fructose and Diabetes. John A. Moorhouse and Robert M. Kark.—p. 46.

The Management of Hepatic Coma in Relation to Protein Withdrawal and Certain Specific Measures. W. H. J. Summerskill, Stanley J. Wolfe, and Charles S. Davidson.—p. 59.

Temporal Lobe Epilepsy: Brief Review: Responses on Electrical Stimulation of the Amygdaloid Region in Six Patients. William P. Chapman, Madan M. Singh, Heinz R. Schroeder, and Charles Fager.—p. 120.

Drug Reactions: Conference on Therapy (Cornell University Medical College).—p. 134.

23, No. 2 (Aug.) 1957

Primary Pulmonary Hypertension. Hiroshi Kuida, Gustave J. Dammin, Florence W. Haynes, Elliot Rapaport, and Lewis Dexter.—p. 166.

Effects of Aminophylline and Diamox Alone and Together on Respiration and Acid-Base Balance and on Respiratory Response to Carbon Dioxide in Pulmonary Emphysema. Morton Galdston and Jack Geller.—p. 183.

* Studies of Neurohypophyseal Function in Man: Diabetes Insipidus and Psychogenic Polydipsia. Joseph F Dingman, Kurt Benirschke, and George W. Thorn.—p. 226.

Gastrointestinal Malabsorptive Syndromes (review). Wade Volwiler.—p. 250.

The Coincidence of Hemoglobin J and Fanconi's Syndrome of Hypoplastic Anemia with Hypoplasia of the Spleen in a Young Man. Marshall E. McCabe, Robert D. Lange, and William H. Crosby.—p. 329.

Fungus Infections Associated with Antibiotic and Steroid Therapy.—The widespread use of antibiotics and of steroid therapy has resulted in considerable anxiety lest fungal infections should complicate such therapy. Torack, in reviewing the autopsy material of the "past three years" at the Montefiore Hospital in New York, found 13 cases of fungus infection with Candida albicans, Aspergillus, or Mucor, discovered at necropsy. All but one of these cases were adult patients; 11 had malignancies as their initial illness, and in 8 of the 13 the primary disorder was hematologic in nature. All 13 patients had had antibiotic and/or steroid treatment prior to death. In five patients the fungal infection resulted only in superficial ulceration of the mucosa of the intestinal tract. None of these patients had had recent steroid therapy, but all five had had antibiotics for between five days and one year prior to death. In contrast, of the eight patients with deep and invasive lesions, all but one had had steroid therapy for between one week and eight and one-half months before death and all eight had received antibiotics for a minimum of two weeks. In two of these eight cases the fungal lesion appeared to be the direct cause of death, in one causing a gangrenous esophagus and in the other resulting in a pulmonary infarction. In another five the fungal lesion was judged to have been a contributory factor to the death. Accordingly, Torack urged great discretion in the combined use of antibiotic and steroid therapy. As explanation for the mechanism by which antibiotics foster such fungal infection, he cites experimental evidence that the antibiotics alter the intestinal flora and also may cause direct tissue toxicity, thereby allowing the fungus to enter via the same route as does the antibiotic. The steroids are felt to contribute to the fungal infection by varying leukocytic activity or by decreasing the production of antibodies.

Fructose and Diabetes.—In a most courageous study, Moorhouse and Kark studied the influence of fructose as compared with glucose in eight patients with diabetes of varying severity. Values of fasting blood sugar, glucosuria, ketone production, and nitrogen balance were determined following withdrawal of insulin therapy and while the patients were taking a standard diet containing mixed carbohydrates. These same determinations (with the exception that the blood sugar specimens were nonfasting) were then made during three five-day periods when the patients were receiving (via indwelling gastric tube) a constant and continuous infusion of Amigen, Lipomul, and vitamins plus carbohydrate—first as glucose, then as fructose, and then as glucose again. The following observations were made: During the fructose period, in all but the severe diabetics, the blood sugar fell to, or toward, the fasting levels obtained during the mixed-carbohydrate-diet period; glucosuria diminished; ketone production ceased or greatly decreased; positive nitrogen balance was restored. Moorhouse and Kark conclude that insulin per se causes but a single metabolic error—the impairment of cellular permeability to the entry of glucose. As a consequence of this abnormality, cellular glucose diminishes and cellular energy starvation follows, with resultant energy metabolism obtained by the breakdown of fat and protein. Fructose, in contrast to glucose, is able to enter the cell even of a diabetic and enters the Embden-Meyerhoff cycle to supply both cell glucose and energy, thereby halting the ketosis and the protein catabolism. That this process occurs in the liver cells is shown by the fact that during a fructose diet high levels of fructose appear in the portal system (rat studies) while none can be found in the arterial or venous blood.

The authors also conclude that a second cellular derangement exists in severe diabetics causing an accelerated hepatic release of cellular glucose. This supposition would explain the failure of fructose to influence favorably a severe diabetic. In such cases all the fructose entering the carbohydrate metabolism of the cell is used to produce glucose, which is promptly discharged into the circulation, and thereby no decrease in ketosis can occur. Finally, the authors explain the failure of fructose to be of any practical clinical value as due, first, to the accelerated cellular release of glucose in severe diabetes and, secondly, to the need for a constant infusion of fructose if cellular starvation is to be prevented.

Studies of Neurohypophyseal Function in Man: Diabetes Insipidus and Psychogenic Polydipsia.—According to recent reports the antidiuretic hormone is produced by a process of neurosecretion in the neurones of certain of the hypothalamic nuclei, is transported along the axones of the supraoptic-hypophyseal tract, and then is either stored in the end-plates about the vascular channels of the posterior pituitary or is secreted directly into these blood vessels. In a study of patients with polyuria, Dingman et al. administered nicotine to test the integrity of the hypothalamic nuclei, which may be activated by noxious agents or by psychic stress as well as by drugs, and hypertonic saline solution to assess the function of the osmoreceptor. In all patients a constant water-loading state was maintained and a good response to vasopressin (Pitressin) excluded renal causes for the polyuria. Three patients showed little or no antidiuretic response to nicotine or hypertonic saline, indicating a loss of neurohypophyseal function. In two the etiology of this failure was obscure; in the other, Hand-Schüller-Christian disease existed. In three subjects with posterior pituitary damage or vascular disease there was a normal antidiuretic response to nicotine but none to the saline solution, which suggested a selective failure of osmoreceptor function, while the hypothalamic neurosecretory tissue remained capable of producing ADH. The authors proposed that either an osmoreceptor, which stimulates the hypothalamic nuclei, may lie in the posterior pituitary or stalk or that ADH, stored in the perivascular regions of the posterior pituitary, is released directly into the blood stream whenever blood perfusing the gland becomes hypertonic. Three patients with psychogenic polydypsia responded normally to hypertonic saline but manifested an elevated threshold for the hypothalamic response to nicotine. Since one of these three evidenced increased adrenal cortical activity and another was receiving cortisone therapy, a relationship between central nervous system excitability and/or adrenal steroid excess and disturbances of hypothalamic function was suggested.

The American Review of Tuberculosis and Pulmonary Diseases, New York

Abstracted by Edwin L. Kendig, Jr.

76, No. 6 (Dec.) 1957

The J. Burns Amberson Lecture: Aerial Dissemination of Pulmonary Tuberculosis. Richard L. Riley.—p. 931.
* Prophylactic Effects of Isoniazid on Primary Tuberculosis in Children: A Preliminary Report; A United States Public Health Service Tuberculosis Prophylaxis Trial.—p. 942.
Electron Microscopic Studies of Mycobacteriophages. Margret Irene Sellers, Kiyoteru Tokuyasu, Zane Price, and Seymour Froman.—p. 964.
A Critical Review of One Hundred and Sixty Consecutive Scalene Node Biopsies. Stewart M. Scott.—p. 1002.
Observations on the Catalase Activity of Tubercle Bacilli. Ruth M. Van Liew.—p. 1007.
β-Propylal-γ-Butylal-Imine: New Substance Having Inhibitory Effect on Mycobacterium Tuberculosis var. Hominis H37Rv. G. Carvajal and E. J. Carvajal.—p. 1094.
The Delayed Appearance of Isoniazid Antagonism by Pyridoxine in Vivo. R. McCune et al.—p. 1100.
Ineffectiveness of Isoniazid in Modifying the Phenomenon of Microbial Persistence. R. McCune et al.—p. 1106.

Prophylactic Effects of Isoniazid on Primary Tuberculosis in Children.—In a cooperative "control study" coordinated by the United States Public Health Service, 2750 children with asymptomatic primary tuberculosis are under observation by 32 clinical investigators. The purpose of this study, which began in January, 1955, is to determine whether small daily doses of isoniazid (4 to 6 mg. per kilogram of body weight) for one year decrease the frequency of immediate complications of the primary disease and the frequency of chronic pulmonary tuberculosis in adolescence and adult life.

In this preliminary report, based on findings up until June 30, 1957, a total of 1394 children in the isoniazid group and 1356 children in the placebo group were observed. During this time, serious extrapulmonary tuberculous complications developed in 5 children who received isoniazid and 26 who received placebo, indicating that isoniazid prevented 80% of the complications of childhood tuberculosis in this group.

Adverse pulmonary changes, less serious in nature, occurred among 21 infected children who received isoniazid and 34 infected children who received placebo, suggesting a favorable effect of isoniazid, although the difference is not significant on a statistical basis.

Children less than one year of age were at the greatest risk of developing tuberculous complications. Children between 1 and 6 years of age were at little risk unless they had positive roentgenographic findings. The only two children more than 6 years of age who developed complications were adolescents.

There is no indication that isoniazid only delayed the appearance of complications.

Annals of Internal Medicine, Lancaster, Pa.

Abstracted by Brian Kiely, M.D.

46, No. 3 (March) 1957

* The Neurologic Manifestations of the Acute Leukemias: A Clinical Study. Charles E. Wells and Richard T. Silver.—p. 439.
A Thrombasthenia Syndrome Associated with Hyperheparinemia. Warren N. Bell and Irving Imber.—p. 537.
Editorial: The Responsibilities of the Medical Profession in the Use of X-rays and Other Ionizing Radiation. Statement by the United Nations Scientific Committee on the Effects of Atomic Radiation.—p. 638.

47, No. 4 (Oct.) 1957

Some Challenging Aspects of Hemoglobin Metabolism. Cecil J. Watson.—p. 611.
Generalized Tetanus: Analysis of 202 Cases. Mario R. Garcia-Palmieri and Ricardo Ramirez.—p. 721.
* Treatment of Tuberculous Meningitis with a Combination of Isonicotinic Acid Hydrazides, Streptomycin and Para-Aminosalicylic Acid. Emanuel Applebaum and Charles Abler.—p. 782.

The Neurologic Manifestations of the Acute Leukemias: A Clinical Study.—Neurologic manifestations were looked for in 63 patients (29 children and 34 adults) with proved acute leukemia admitted to the National Cancer Institute and were found in 24 cases. There was no relationship of their incidence to the cell type or age. The commonest neurologic complication was intracranial hemorrhage, which occurred in 12 patients, most of whom had very low platelet counts. In 11 cases neurologic signs were attributed to leukemic infiltration, although, as has been noted by others, the pathologic findings often appeared inadequate to explain the clinical findings. In this group the latter included evidence of increased intracranial pressure, impairment of consciousness, convulsions, meningismus, pleocytosis, pyramidal tract signs, involvement of the basal ganglia and hypothalamus, and cranial and peripheral nerve pareses. Seven patients improved neurologically on treatment with 6-mercaptopurine, Methotrexate, and cortisone, although two of them showed no hematologic response. In one case the neurological manifestations occurred while the patient was in hematologic remission but responded to treatment, nevertheless.

One patient developed bacterial meningitis due to Staphylococcus pyogenes var. aureus. Of four patients classed as miscellaneous two had psychoses, one of which was due to cortisone.

Treatment of Tuberculosis Meningitis with a Combination of Isonicotinic Acid Hydrazides, Streptomycin, and Para-Aminosalicylic Acid.—Forty-one patients, more than half of whom were under 10 years of age, were treated with isoniazid or iproniazid in doses of 10 mg. per kilogram in the acute phase and 5 mg. per kilogram in the late convalescent phase in most instances, streptomycin in doses of 1 gm. daily in the acute phase in most cases, and aminosalicylic acid usually in doses of 6 to 12 gm. daily in the acute phase. The patients had typical clinical and laboratory evidence of tuberculous meningitis which had been present for two days to two months prior to treatment, and most of them were critically ill. A positive bacteriologic diagnosis was established in 36 cases.

Twelve patients, four of whom were moribund on admission, followed a generally downhill course or showed only temporary improvement and died. Six of these were autopsied; five had miliary tuberculosis, and one had extensive cerebral infarction. The remaining 29 showed remission of fever, improvement of the mental state, regression of meningeal signs, and weight gain in about two or three months. Thereafter, improvement progressed slowly, often interrupted by febrile episodes, and there were complications such as spasticity, paresis, visual impairment, deafness, incontinence, decubitus ulcers, and bladder calculi. Relapses occurred after discontinuance of therapy in two cases but never during treatment. Side-reactions, infrequent in this series, were noted in 10 patients and were attributed to the hydrazide in 2. Of the 29 survivors, who were observed for periods of 4 to 54 months, 4 have serious neurological sequellae, including severe spasticity, mental retardation, and optic atrophy and 5 have lesser degrees of muscular spasm and paresis.

The study does not show clearly what factors influence the outcome, although early treatment, adequate dosage, and relative mildness of the case seem to play a role. The superiority of this form of treatment to streptomycin alone, which was attended in the past by a high rate of relapse, is obvious. Compared with a previous small series (10 patients) treated with hydrazides alone, the regimen described here shows no superiority in morbidity or mortality. Apparently hydrazides are the drug of choice, and their use as the sole agent for treating tuberculous meningitis merits further trial.

Archiv für Kinderheilkunde, Stuttgart

Abstracted by Werner K. Gottstein, M.D.

155, No. 1, 1957

Localized and Generalized Tics and Their Treatment. E. Geisler.
* Moro Reflex and Startle Reactions in Infants. S. Wiesner, K. Domanowsky, and G. Heinen.
On the Prophylaxis of Streptococcal Infections. F. Küster and E. Sauter.
Transitory Acute Inhibition of Erythropoiesis During Infantile Infections. J. Goetz.
Arteriovenous Angiomas in the Brain in Infants. K. Decker and W. Freislederer.
Fulminant Purpura Following Chickenpox. H. Radl and K. Hekele.
On Prenatal Renal Function: Illustrated by a Significant Anomaly of Renal and Ureteral Organs. E. Zapp.
On Fat Storage Disease of the Liver. H. Kleinbaum.
Foregut Cysts in Infancy. H. Roemer and G. Mollowitz.
On the Differential Diagnosis of Actinomycosis of the Mandible. H. Uhlig.

155, No. 2, 1957

Day-Night Rhythm: Effect of Carbonanhydrase Inhibitor on Water-Electrolyte Secretion; Relation to Other Functional Renal Tests. A. Rosenkranz and W. Swoboda.
The New Law on Food: Its Significance for the Pediatrician. E. Mueller.
On the Treatment of Burns in Childhood. H. Versé.
* Encephalomyocarditis Syndrome, Associated with Other Organic Diseases. K. Mueller.
On the Evaluation of Success of Climate-Saltwater Treatment in Labile Vegetative Children. K. Kleinschmidt.
On Bronchostenosis and Bronchial Occlusions in Childhood. H. J. Dietzsch.
Purinethol Poisoning in Childhood. H. Polster.

155, No. 3, 1957

Blindness After Measles. H. Moll.
The Significance of the Goldsol Curve in Childhood. J. Weber.
Frequency of Infections in Prematures. R. Degen.
* On Influenza Myocarditis in Childhood. N. Mueller.
Differential Diagnosis of Chronic Familial Renal Diseases in Childhood. R. Gruettner and W. Lenz.
On Essential Hemosiderosis of the Lungs. W. Leschke and S. Wagner.
Treatment of Essential Erythroblastopenia by Prednisone. L. Brockhaus.
Arterial CO_2 Determination of Infants, Calculated from Values of Superior Sagittal Sinus. J. Wenner, R. Beer, and E. Doll.
* Schoenlein-Henoch Purpura and Its Associated Renal Complications. R. Nordman.
Concentration Test and Renal Function in Early Childhood: Determination of Specific Gravity of Small Urine Samples After Krutzsch. G. Marquardsen and J. Jochims.
On Liver-Damage Tests in Hepatic Tuberculosis of Children. K. Dietel and C. Nachtigall.
On Rickets Prophylaxis of Prematures. S. Evers.
Potassium Values of Red Blood Cells in Hypertrophic Pyloric Stenosis. W. Albrecht.
Unusual Complication of an Umbilical Infection. I. Peckholz.
On Damage to Organs by Intensive Prophylactic Rickets Treatment. W. Schubert and W. Kleint.

156, No. 2, 1957

The Diagnosis of Defects of Coagulation. M. F. Hoerder.
* Differential Diagnosis of the Acute Abdomen in the Newborn. H. G. Wolf.
Contribution to the Diagnosis of the Eosinophilic Granuloma. W. Mueller-Rentzsch.
On Multiple Malformations Resulting from Anomalies of the First Visceral Arch. O. Hoevels and J. L. Morlinghaus.
On Pasteurella Pseudotuberculosis or Rodentiosis in Humans. W. C. Hecker.
On the Early Stages of Incontinentia Pigmenti (Bloch-Sulzberger). W. Schulze and M. Noack.
Late Complications After Smallpox Vaccination in the Course of Otogenous Sepsis. W. Kiehl and J. Potel.

Moro Reflex and Startle Reactions in Infants.—In 23 healthy infants cinematographic recordings of the Moro reflex were taken. This analysis revealed that this reflex is composed of an initial clonic phase and a slow tonic phase. The first phase represents the character of the muscular contraction, limitation to the flexor muscles, tendency to involve neighboring segments, obviously a protectional reflex. The second phase, with much longer delay and reaction time, consists of a tonic spreading movements of the limbs, followed by an adduction to the axis of the body.

Encephalomyeltis Syndrome, Associated with Other Organic Diseases.—The combination of encephalomyelitis and myocarditis with clinical and electrocardiographic manifestations has been observed more frequently in recent years in all countries. It was impossible to relate this associated entity to a specific virus form. The author reports about experiences where, besides this syndrome, renal and hepatic alterations became apparent.

On Influenza Myocarditis in Childhood.—During an influenza epidemic six children were affected by a myocarditis that developed 10 to 30 days after the primary infection. The onset was sudden, with loss of appetite, extreme pallor, restlessness, cyanosis of lips, tachycardia, and tachypnea. Serial ECG's indicating depressions of ST segments illustrate the gradual improvement after 6 to 12 months. Initially, the manifestations were sometimes alarming, required oxygen and Strophantin injections. Favorable responses to combined treatment of phenylbutazone (Butazolidin) suppositories and cortisone were significant in three cases.

Schoenlein-Henoch Purpura and Its Associated Renal Complications.—Detailed analysis is presented of 105 cases of Schoenlein-Henoch purpura that were observed in the Children's Hospital of the University of Turku between 1945 and 1956. The incidence has increased, especially during the winter and within the age group of 2 to 4 years. In 15% of the cases allergic manifestations occurred prior to the outbreak. Seventy children suffered from infections. In 14 patients hematuria and albuminuria were found, but the nephritic signs persisted only in 1. Follow-up tests of the renal functions failed to reveal permanent damage.

Differential Diagnosis of the Acute Abdomen in the Newborn.—This is a very important and instructive paper, reporting a thorough study performed at the University Children's Hospital in Vienna. The European as well as the American literature is properly evaluated. Clinical and x-ray studies (very satisfactory reproductions) enabled the author to arrive at definite diagnostic conclusions at an early period of life. The type of abdominal distention, the evacuation disturbance of the meconium, and films, mostly without oral contrast media, were especially helpful in the differentiation of megacolon, spontaneous pneumoperitoneum, and meconium ileus and in making the distinction between duodenal atresia and physiological meteorism.

Boletín médico del Hospital Infantil, Mexico, D. F.

Abstracted by Mary Allen, M.D.

14, No. 4 (Aug.) 1957

Editorial: Responsibility of the Medical Profession in the Use of X-Rays and Other Radioactive Devices.—p. 335.
Rural Center Affiliated with Children's Hospital at Tlaltizopan, Morelia, Mexico: Preliminary Information. Federico Gomez, Raphael Ramos Galvan, Joaquin Crovioto, and Silvestre Frenk.—p. 341.
Carob Flour in the Treatment of Diarrhea in the Premature Infant. J. Alvarez de los Cobos, E. Jurado Garcia, and Josefine Sagaon.—p. 348.
Neoplasms in Children: Neoplasms of the Testicle. Maximiliano Sales, Antonio Villasana, and Y. Jesus Villegas.—p. 359.
Rickets in a 4-Year-Old Girl. Luis Gomez-Orozco.—p. 427.
A Case of Congenital Stenosis of Intestine with Associated Malformations.—p. 437.

14, No. 5 (Oct.) 1957

Occupational Dermatitis in Nurses from a Premature Service. Luis Gomez Orozco.—p. 493.
Therapeutic Possibilities and Limitations of a New Topical Corticosteroid in Dermatology. Jose Luis Cortez and Silvia Radillo.—p. 513.
Trichobezoar in Children: Report of 4 Cases. Carlos Sarinana, Arturo Silva Cuevas, Hector Manuel Quintero, and Jorge Velasco Alzaga.—p. 523.
Two Cases of Fasciola Hepatica in Early Stages as a Diagnostic Problem. Francisco Biozi, Raphael Soto, Samuel Dorantes, Techruciano Olga Castrejon, and Jaime Portilla.—p. 533.
* The Use of Dextran in Nephrotic Edema. Carmen Gil Nota, Raphael Soto Allande, and Gustavo Gordills Paniagua.—p. 545.

The Use of Dextran in Nephrotic Edema.—The authors discuss the significance of edema in nephrosis. Although the treatment of the edema may not modify the course or the prognosis of the disease, it is necessary to treat the symptom. They feel that diuresis should be attempted before the use of steroids.

There are six different groups of treatments which attack the problem in different ways. They are (1) agents which diminish the absorption of the Na^+ ion, such as diets low in salt and resins for exchange of cations; (2) agents which diminish the renal reabsorption of Na^+, such as mercurial diuretics, ammonium chloride, urea, and inhibitors of carbonic anhydrase; (3) methods designed to correct electrolytic imbalance, such as alkaline salts of sodium and potassium; (4) mechanical removal of ascites by paracentesis; (5) endocrine products, such as thyroid and anterior pituitary extracts; (6) agents which elevate the oncotic pressure of plasma, such as gelatin, concentrated human albumen, acacia, etc. Among the devices which

are alleged to affect the plasma is dextran, which the authors tried in 10 children with the nephrotic syndrome.

The details of the treatment and results are well tabulated. Seven children improved.

The authors conclude that dextran by expansion of plasma, as was shown by the lowering of the hematocrit value, is valuable in the treatment of nephrosis.

There were minimal undesirable effects such as transitory hypertension in three children and mild transitory hematuria in another case.

The diuresis which followed the use of dextran is due to the increase in plasma volume, which increases the velocity of glomerular filtration and inhibits the production of antiduretic hormone.

Canadian Medical Association Journal, Montreal

Abstracted by H. M. Keith, M.D.

77 (Oct. 15) 1957

An Outbreak of Asian Influenza in a Girls' Camp. A. W. Rebhan.—p. 797.

77 (Nov. 1) 1957

* A Survey of the Incidence of Resistance to Antibiotics in Bacteria Isolated in a Children's Hospital. T. D. Roy, Anne M. Collins, Grace Craig, and I. B. R. Duncan.—p. 844.
The Role in the Community of a Mental Deficiency Clinic. R. Gibson.—p. 878.

77 (Nov. 15) 1957

Studies in Stillbirths and Neonatal Deaths in Winnipeg: II. Definitions in Perinatal Mortality. A. J. D. DePape, E. J. N. Briggs, Georgina Hogg, J. R. Mitchell, and H. Medovy.—p. 963.

77 (Dec. 15) 1957

Recurrent Otitis Media in Children (editorial).—p. 1121.

78 (Jan. 1) 1958

Needless Loss of Vision: Its Prevention. F. W. Law.—p. 1.
* Deafness in Children. J. A. Rubin.—p. 51.

A Survey of the Incidence of Resistance to Antibiotics in Bacteria Isolated in a Children's Hospital.—The increase in incidence of antibiotic-resistant strains of organisms throughout our various communities is now well recognized. The authors have studied this in numerous strains of Staphylococcus pyogenes, Escherichia coli, Proteus mirabilis, Pseudomonas aeruginosa, and several other organisms, including Hemophilus influenzae.

It has been a common finding that in treating staphylococcic infection, the more an antibiotic is used the more rapidly do resistant strains of staphylococci become prevalent. In addition, after the increase in resistant strains has continued for a few years an equilibrium seems to develop. They note that staphylococci, in the Hospital for Sick Children, had reached an equilibrium in resistance to penicillin and streptomycin by 1952, and the incidence of resistant strains in all the species tested has in general remained constant over the five-year period 1952-1957. To measure resistance they used the disk plate method, using disks of three different strengths for each antibiotic. The method must be carefully supervised, as a change in concentration of the disks altered the interpretation considerably.

With the tetracyclines the plateau was reached in 1953, and there was a further increase in resistant strains in 1955 after the introduction of tetracycline. They also note that there was a small rise in resistance of staphylococci to erythromycin, but the level of resistance to both erythromycin and chloramphenicol remained low in their hospital. Staphylococci from outpatients in the hospital seemed generally more sensitive to antibiotics than strains from inpatients. This difference between outpatients and inpatients was more noticeable when E. coli was tested, the resistance to E. coli being probably limited to hospitals where cross infections occur. Hemolytic streptococci (Lancefield Group A) and pneumococci remained uniformly sensitive to penicillin, to the tetracyclines, and to chloramphenicol. H. influenzae also remained fully sensitive to chloramphenicol and the tetracyclines.

Deafness in Children.—One hundred consecutive patients referred because of hearing difficulty are reviewed. There were 53 cases of conductive deafness, 19 of nerve deafness, 25 mixed, and 3 children with normal hearing. Postnatal causes of deafness outnumbered

prenatal causes 9:1. Otitis media is the major cause. Tonsillectomy and adenoidectomy should be done in all cases of recurrent otitis media. Radiation of the nasopharynx is indicated to shrink lymphoid tissue around and in the Eustachian orifices that remain blocked despite tonsillectomy and adenoidectomy.

Journal of the American Medical Association, Chicago

Abstracted by Don M. Hosier, M.D.

166, No. 4 (Jan. 25) 1958

* Roentgen Evidence of Normal Heart and Congenital Abnormality in Early Infancy. James Carter, George Cooper Jr., Frank Dammann, and Fred Mitchell.—p. 337.
Lobar Emphysema. H. W. Fischer, J. L. Lucido, and C. P. Lynxwiler.—p. 340.
Current Status of Therapy in Bacterial Endocarditis. Maxwell Finland.—p. 364.

Roentgen Evidence of Normal Heart and Congenital Abnormality in Early Infancy.—Respiratory distress in a newborn infant is frequently encountered, and a chest roentgenogram is often obtained. Factors that make it difficult to interpret cardiorespiratory difficulties in the newborn infant were studied by reviewing 1000 chest roentgenograms obtained within 24 hours after birth. Two technical factors were found to prevent uniformity: It was difficult to eliminate rotation in a lively infant, and the technician could not always make the exposure at the height of inspiration. The large size and anterior location of the thymus added to the difficulty created by the high position of the diaphragms. The cardiothoracic ratio was generally rendered worthless as a diagnostic aid.

In the presence of clinical evidence of congenital heart disease, rough determination of heart size and shape can be better made by fluoroscopic than by roentgenographic examination. The authors state that most cyanosis in the first 24 hours of life is caused not by heart disease but by pulmonary pathology. Attention must be paid to the distribution of cyanosis and the presence of murmurs, abnormal pulsations, or rales. Achrocyanosis of the hands and feet is of no clinical significance. Deep cyanosis of the lips and nail beds and cyanosis of the face and trunk indicate pulmonary or cardiac pathology. They emphasize that it is only when there is clinical evidence of cyanotic congenital heart disease that roentgenographic findings are of some value.

The conclusion reached is that it is not actually possible to define the limits of normal for the cardiac shadow in the newborn infant; any concern about the heart aroused by the chest roentgenogram obtained during the first 24 hours of life should not be shared with the parents until the presence of an abnormality is substantiated by other findings.

Medizinische Klinik, Munich

Abstracted by Samuel Amberg, M.D.

52, No. 32, 1957

* Pulmonic Hyaline Membrane and Respiration of the Newborn. H. Wulf.—p. 2246.

52, No. 49, 1957

* Results with a New Sedative in Children. H. Becker.—p. 2122.
Treatment of Epilepsy with Bargosin-Natrium. H. G. Koslowsky.—p. 2128.
* The Significance of the Placental Circulation for the Exchange of Substances Between Mother and Child. H. W. Kayser.

52, No. 50, 1957

* Rectal Bismuth Treatment of Anginas in Childhood. B. Schillert.—p. 2167.

52, No. 51, 1957

The Acute Otitis Media of the Infant. R. Schroer.—p. 2113.

52, No. 52, 1957

* Diagnostic Errors in Cases of Attacks Due to Cerebral Organic Involvement in Childhood. F. Specht.—p. 2233.

53, No. 1, 1958

* Arrest of Development as Consequence of Deficient Care of Children. U. Koettgen.—p. 1.
* Fundamentals of Antibiotic Therapy Illustrated by the Treatment of Pneumonia in Children. H. Mueller.—p. 25.

Pulmonic Hyaline Membrane and Respiration of the Newborn.—Guinea pigs and rats were exposed for various periods of time to low-oxygen air and to high oxygen pressure. Hypercapnia was induced with air-carbon dioxide and carbon dioxide-oxygen mixtures. Animals were rendered acidotic by administration of ammonium chloride or sodium chloride. When exogenous carbon dioxide was increased, pulmonic hyaline membranes were formed. This also happened with exposure to excessive oxygen, a procedure which induces a hypercapnia in the terminal stages. When the stage of hypercapnia is not reached, no hyaline membrane is formed.

The factors in the production of hyaline membrane in the newborn are discussed, particularly in relation to its prevention.

Results with a New Sedative in Children.—A mixture commercially obtainable under the name of Miramel was used. The honey is produced by bees with access to extracts of valerian, woodruff (Asperula odorata), and melissa, plants to which a sedative action has been ascribed. In addition, it contains a methylparafinol, a tertiary unsaturated aliphatic alcohol which is known under its trade name Dormison. It is to be noted that the exact composition of Miramel is not given. It has been given to about 250 children 9 months to 12 years of age in a dosage of about 3 to 6 teaspoonfuls daily, increasing with age. At about six years of age dosage is from about 6 to 8 teaspoonfuls. Its good taste is of advantage. Initial difficulties of behavior associated with hospitalization were eliminated promptly. Hyperirritability due to various reasons also was benefited as a rule, even when treated at home. The medication could be omitted after a few days. It could be administered in the course of a number of diseases, without interfering with other treatment. It is claimed that no untoward reactions were observed.

The Significance of the Placental Circulation for the Exchange of Substances Between Mother and Child.—The conditions of the blood circulation of maternal and fetal placenta are discussed, particularly with regard to the distribution of substances which can pass the placental barrier in either direction. It is emphasized that as little time as possible should intervene between narcosis and delivery. This interval should not exceed 10 minutes. Under these conditions, the author states, he has never observed an influence of the narcosis on the newborn.

Rectal Bismuth Treatment of Anginas in Childhood.—A number of children, 1 year to 14 years of age, with angina catarrhalis, angina follicularis, and angina lacunaris were treated with suppositories of Bismogenol, containing 50 mg. of bismuth as bismuth camphocarbonate. Depending on age, 1½ to 4 suppositories were given in a period of 24 to 36 hours. No side-reactions were noted. Fever ceased in one to two days—a few times in three days. Subjective improvement was noted after the first day. Only 1 case of otitis media purulenta occurred among the 41 patients, and 2 cases did not respond to the treatment; 1 of them had infectious mononucleosis and the other a severe general disturbance of unknown origin. Attention is called to a synergism of bismuth and penicillin.

Diagnostic Errors in Cases of Attacks Due to Cerebral Organic Involvement in Childhood.—The paper deals mainly with "larvierten hirnorganischen Anfaellen," which have been described as "masked epilepsy," most of which belong to the group of psychomotoric epilepsy of Gibbs and Lenox. Cases are described, with emphasis of the importance of keeping in mind the possibility of masked epilepsy in cases in which there are obscure seizures of pain, disorders of concentration, enuresis, respiratory affect spasm, too frequent stumbling of young children, and collapse-like symptoms, even when disturbances of consciousness are denied. It is important to obtain a very careful history. Electroencephalic examination is necessary, and not infrequently careful observation must be made in the hospital by trained personnel. Anticonvulsant medication proved effective; the choice of drugs is not mentioned.

Arrest of Development as Consequence of Deficient Care of Children.—It is to be noted that the term "Verkuemmerung," introduced by the author, denotes an element of deterioration in addition to that of arrested development. The tendency to arrive at summary conclusions without due consideration of other factors is deplored. The influence of lack of proper care in institutions on psychic and physical development is discussed. Attention is called to the difference in individual disposition to react to such a lack of care. Under the conditions prevailing, short hospitalization is not likely to cause lasting damage. Prolonged

institutionalization in hospital or home may lead to long-lasting difficulties in a few illustrative cases of institutionalization extended over more than two years.

Fundamentals of Antibiotic Therapy Illustrated by the Treatment of Pneumonia in Children.—The determination of the pathogenic micro-organisms is demanded preceding any antibiotic therapy. Prophylactic administration is only permissible exceptionally, as in rheumatic endocarditis and to prevent spread of scarlet fever in institutions. The problem of resistant strains is discussed. Uncomplicated cases of pneumonia in children were treated with penicillin. One group received only depot penicillin; another, water-soluble crystalline potassium penicillin G intramuscularly. The dosage was 40,000 units per kilogram per day. According to the determination of the blood level, this level must have been insufficient for many hours. Nevertheless, the average temperature curve and the disappearance of the clinical symptoms were identical in the two groups. Another group received phenoloxymethylenpenicillin (Oratren) orally, about 12,000 to 15,000 units per kilogram per day, which has the advantage of producing allergic reactions very rarely. This last group received only one-third of the penicillin given to the children of the other two groups. The ages of two-thirds of the children fell into the first and second years of life. The Oratren was given in five divided doses. Repeated relatively small doses of this penicillin given by mouth proved as efficient as the larger injected doses. This dosage of 15,000 units per kilogram per day proved also satisfactory in cases of scarlet fever, lymphadenitis, and pyuria due to cocci. The aim of the antibiotic treatment should be usage of oral medication as much as possible and a dosage as great as needed but as small as possible.

Neue Oesterreichische Zeitschrift für Kinderheilkunde, Vienna

Abstracted by Hermann Vollmer, M.D.

Vol. 2, 1957

* New Observations on a Case of Typus Degenerativus Amstelodamensis (Cornelia de Lange). Ernst Zweymüller.—p. 40.
* Personality Studies in Obese Children. Ernst Huber.—p. 186.

New Observations on a Case of Typus Degenerativus Amstelodamensis (Cornelia de Lange).—This is the ninth case reported in the European literature of a syndrome of congenital anomalies first described by Cornelia de Lange as typus amstelodamensis. Mental retardation, brachycephaly, deep insertion of the ears, exaggerated eyebrows and long eyelashes, proximal position of the thumbs, and syndactyly are regarded as obligatory symptoms of this syndrome, which has been observed in seven girls and two boys. In addition, Zweymüller describes in his case synophrys, slit eyes, blue sclerae, horizontal nystagmus, short nose with a broad bridge and the nostrils turned forward, thin lips, luxation of the radius head resulting in restricted extension in the elbow (observed in other cases), short hands with simian lines, hypotonic muscles, and hypospadias. Radioiodine uptake was 1% but increased to 20% after injection of thyrotropin. This "pituitary hypothyroidism" coincided, however, with a normal bone age. Extensive roentgenographic studies revealed multiple minor skeletal anomalies, different from those in Mongolism. EEG was normal. The Sabin-Feldman test for toxoplasmosis was found positive, but this was regarded by the author as coincidental.

Personality Studies in Obese Children.—Fifty obese children and fifty normal controls of equal age and sex distribution, equal socioeconomic background, and equal scholastic success were examined by careful anamnesis and psychometric tests, and the results were statistically evaluated. Familial incidence of obesity, overeating, inactivity, lack of initiative, laziness, preference of sedentary hobbies, and social difficulties were significantly more prevalent in the obese group. There was no significant difference between the two groups with regard to intelligence, memory, perseverance, dexterity, fantasy, and average scholastic performance. In contrast to Hilde Bruch's findings, overprotection was not found to be a significant factor, and the social difficulties are regarded as a result rather than cause of the obesity.

Pediatrics, Springfield, Ill.

Abstracted by William W. Cleveland, M.D.

20, No. 3 (Sept.) 1957

Milk Allergy: I. Observations on Incidence and Symptoms in "Well" Babies. K. D. Bachman and S. C. Dees.—p. 393.

Milk Allergy: II. Observations on Incidence and Symptoms of Allergy to Milk in Allergic Infants. K. D. Bachman and S. C. Dees.—p. 400.

Primary Pulmonary Hypertension. H. S. Rosenberg and D. G. McNamara.—p. 408.

Chediak-Higashi Syndrome: A Lethal Familial Disease with Anomalous Inclusions in the Leukocytes and Constitutional Stigmata: Report of a Case with Necropsy. W. L. Donohue and H. W. Bain.—p. 416.

A Syndrome of Recurrent Infection and Infiltration of Viscera by Pigmented Lipid Histiocytes. B. H. Landing and H. S. Shirkey.—p. 431.

Salmonella Osteomyelitis and Abnormal Hemoglobin Disease. H. K. Silver, J. L. Simon, and D. H. Clement.—p. 439.

* On the Acceptance of Solid Foods, and Other Food Patterns, of Infants and Children. V. A. Beal.—p. 448.

Poliomyelitis Viremia in a Newborn Infant. J. Winsser, M. L. Pfaff, and H. E. Seanor.—p. 458.

The Distribution of Group B Coxsackie Viruses in a Children's Institution. J. C. Rivadeneira, F. C. Robbins, M. Crea, and R. M. Eiben.—p. 468.

The Effect of Humidity on Survival of Newly Born Premature Infants. W. A. Silverman and W. A. Blanc.—p. 477.

The Adrenogenital Syndrome, Salt-Losing Type: Case Reports of Two Males with Prolonged Observation Since Birth. H. K. Faber.—p. 488.

Nonadrenal Female Pseudohermaphrodism After Administration of Testosterone to Mother During Pregnancy: Report of a Case. E. Grunwaldt and T. Bates.—p. 503.

In Vitro Comparison of the Antithrombic Action of Heparin and Chondroitin-Sulfuric Acid-B. B. J. Grossman and A. Dorfman.—p. 506.

Ultramicro Determination of Salicylates in Blood Serum. R. P. MacDonald, J. Ploompuu, and E. M. Knights Jr.—p. 515.

On the Acceptance of Solid Foods, and Other Food Patterns, of Infants and Children. An analysis of the nutritional histories taken on 65 children in the period from 1946 to 1955 is presented. A definite trend toward earlier introduction of foods other than milk is reported, but the number of infants refusing to accept solid feedings is noted to have increased. The "average age of willing acceptance" is reported as follows: cereals, 2 to 2½ months; vegetables, 4 to 4½ months; meat and meat soups, 5½ to 6 months; and fruit, 2½ to 3 months. A review of hematologic measurements made on these children indicated no beneficial effect of a higher intake of iron as offered by early feeding of cereals.

A rapid and smooth increase in intake was noted in early infancy, with a marked decrease in appetite in the preschool period. These changes are accompanied by similar increases in calorie intake while protein intake reaches a plateau at from approximately 1½ to 3½ years of age and is followed by a slow rise; calcium intake reaches a peak at approximately 6 months of age and falls off rapidly in the preschool age, to rise slowly in the older child.

Presse médicale, Paris

Abstracted by Jeana Levinthal, M.D.

65 (May 15) 1957

* Abnormalities of the Bone Marrow in the Course of Rheumatic Fever and Infections Due to Hemolytic Streptococci. M. Bernheim, C. Mouriquand, and D. Germain.—p. 907.

65 (May 22) 1957

A Case of Stevens-Johnson Syndrome After Smallpox Vaccination. Y. Boquien, D. Hervouet, G. Dauphin, R. Lhermitte, and C. Robin.—p. 956.

65 (June 8) 1957

Cytology of the Pancreas in Two Twin Four-Month Fetuses Born to a Diabetic Mother. A. Geyer and J. Staeffen.—p. 1079.

65 (June 26) 1957

* Late Spondylo-Epiphyseal Dysplasia: Clinical and Radiological Description. P. Maroteaur, M. Lamy, and J. Bernard.—p. 1205.

Complete Congenital Absence of the Femur with Tibio-Cotyloid Connection. L. Michel. p. 1213.

65 (July 27) 1957

Icterohemorrhagic Syndrome of the Newborn with Anoxia and Shock: Relationship to Generalized Cytomegalic Inclusion Disease. J. Cathala, S. Poupinet, and A. Mouv.—p. 1337.

65 (Aug. 24) 1957

* Treatment of Infantile Obesity with Hydro-Oxazine (Preludin). J. Weill and Bernfeld.—p. 1401.
* Contribution to the Therapy and Prognosis of Tuberculous Meningitis in Children. A. Saim, P. Radovici, M. Rierbineanu, M. Fruhling, N. Gheorghiu, G. Netedu, and E. Scurei.—p. 1403.

65 (Sept. 28) 1957

* BCG Test "Accompanying" BCG Vaccination. E. Bernard, Cros-Decam, and Le Joubioux.—p. 1547.

65 (Oct. 9) 1957

* Infant Diarrhea Due to E. Coli: Influence of Breast Feeding. A. Lambrechts, H. Hainaut, and M. Nicolas-Goldstein.—p. 1607.

65 (Oct. 30) 1957

Intolerance to Gluten. G. Pathe and A. Morel.—p. 1754.

65 (Nov. 6) 1957

Treatment of Leprosy by D. Cycloserine (Oxamycine). M. Pestel and L. Chambon.—p. 1791.
* Catheterization of the Left Side of the Heart by Direct Puncture. R. Raynaud, J. Houel, M. Brochier, P. Callige, and P. Morand.—p. 1793.

65 (Nov. 23) 1957

* Polymyxin Treatment of Infantile Diarrhea Due to E. Coli Resistant to Other Antibiotics. F. Lutier and R. Dalbeuf.—p. 1905.
A Case of Sarcoidosis of the Central Nervous System. R. Garcin, R. A. Marquezy, J. Lapresle, C. Bach, and J. C. Dayras.—p. 1926.

65 (Nov. 30) 1957

Normal Hepatic and Splenic Arteriography by Venous Route in Children. C. Sarrouy, L. Sendra, and G. Legeais.—p. 1963.

65 (Dec. 7) 1957

* Acute Eczema Due to Mercury Sensitivity. P. Vermenouse.—p. 2021.

65 (Dec. 14) 1957

* Remissions in Acute Leukemia. J. Olmer and A. Murisasco.—p. 2057.

65 (Dec. 21) 1957

* Danger of Hyperimmune Serum in the Treatment of Pertussis. A. Plichet.—p. 2123.

Abnormalities of the Bone Marrow in the Course of Rheumatic Fever and Infections Due to Hemolytic Streptococci.—In 130 cases of rheumatic fever, 184 bone marrow examinations were performed. A plasmocytosis averaging 5.6%, but sometimes reaching 15%, was the most consistent finding, but a lymphocytosis greater than that to be expected for the child's age, and sometimes reaching 50%, was often present. Treatment with steroids reduces the medullary plasmocytosis to normal limits in 8 to 10 days as judged by those children (number not stated) where repeated bone marrow examinations were performed. Those not treated with steroids still showed a plasmocytosis after two to four weeks. In 18 cases of chorea, there was plasmocytosis only in those cases complicated by endocarditis. In 16 cases of scarlet fever, there were a marked initial eosinophilia and an average plasmocytosis of 3.6%. In 28 cases of nephritis, the bone marrow was normal in late cases and in acute cases following skin infections but plasmocytosis (up to 7.2%) was found in acute cases associated with Streptococcus infections.

Late Spondylo-Epiphyseal Dysplasia: Clinical and Radiological Description.—Jacobson described in 1939 a disease affecting 20 members of one family, which he termed hereditary deforming osteochondrodystrophy. The authors have collected 10 similar cases, which they differentiate from other similar malformations and especially Morquio's disease, due to the late onset, the predominance of the spinal changes, their x-ray appearance, and the occasional involvement of the hip, with malformations leading to frequent arthroses in subjects over 40. The vertebral bodies are flattened, the thorax is short, with increased anteroposterior diameter and failure of growth is noted at adolescence. The syndrome appears to be sex-linked recessive, affecting males.

Treatment of Infantile Obesity with Hydro-Oxazine (Preludin).—Sixty children aged 2 to 15 years, (average 12 to 14 years) were studied. Forty were given Preludin, 1 to 3 tablets (25 mg.) daily and allowed to eat what they pleased; twenty were given Preludin plus qualitative instructions to avoid sweets and starchy and fatty foods. A control group of 20 obese children were given quantitative diet instruction alone. Children receiving Preludin alone lost, on the average, 2% to 5% of the initial body weight in the first month, with a cumulative total of 8% to 10% at the end of six months. Those treated with Preludin plus diet instruction lost 5% to 11% in the first month and up to 20% in four or five months; normal weights were generally achieved before six months of observation. Those treated by quantitative diet instruction lost more weight than either of the other groups. It is interesting to note that the children given Preludin alone promptly regained weight when the medication was stopped, since their food preference was generally for starchy foods and sweets. The authors emphasize the inadequacy of treatment by medication alone, with the danger of insufficient consumption of protein by the growing child; they find it useful as an addition at times when weight loss has slowed because the child has become tired of following his diet and needs the psychologic encouragement of further weight loss.

Contribution to the Therapy and Prognosis of Tuberculous Meningitis in Children.—In two groups of cases of tuberculous meningitis in children aged 0 to 12 years, totaling 170 cases treated from 1952 to 1955, the authors draw the following conclusions: 1. Isoniazid is superior to streptomycin. 2. Therapeutic results depend upon early diagnosis and the mode of administration of isoniazid. 3. Isoniazid in doses of 20 mg. per kilogram of body weight, without intrathecal therapy and with the addition of streptomycin by injection, resulted in 100% cure of 30 cases diagnosed early. 4. Doses of 5 to 10 mg. per kilogram of body weight of isoniazid given to 70 comparable cases in the two preceding years, along with intrathecal therapy and streptomycin, resulted in a mortality of 7.1%, and complications in 25.7% of those surviving.

BCG Test "Accompanying" BCG Vaccination.—A BCG intradermal test with heat-killed BCG vaccine at the time of BCG vaccination (live BCG) can be helpful, since the skin test becomes positive when the vaccination "takes" and the child has developed sensitivity to BCG protein. In persons free from tubercular sensitivity there may be a nonspecific papuloerythematous reaction to the killed BCG test, reaching its maximum at 24 to 48 hours but rarely exceeding 8 mm. in diameter. In contrast, in persons already sensitive, the reaction begins in the first 24 hours but reaches its maximum in 3 to 5 days and may progress to central ulceration and crusting in 2 to 15 days. In children vaccinated with BCG after being proved free of tuberculosis, who are given an "accompanying" intradermal injection of heat-killed BCG, over 90% will show a positive reaction at the site of the skin test in three to six weeks, consisting of a local lesion which is either papuloerythematous, papuloerythematous with a yellow center, or ulcerated. Where children have been separated from a tuberculous environment and given BCG, the appearance of the "accompanying" reaction is proof of a "take." If the test is done prior to vaccination, it is doubly helpful, since the single injection screens for prior tuberculous infection, and later proves the success of the vaccination.

Infant Diarrhea Due to E. Coli: Influence of Breast Feeding.—In an epidemic of infant diarrhea due to E. coli O11-B$_4$ in a hospital nursery, 13 infants were breast-fed, and 11 were given cow's milk. The severity of the disease and the mortality were the same in both groups, and no protective or therapeutic influence was noted in the use of human milk for the sick baby.

Catheterization of the Left Side of the Heart by Direct Puncture.—Coupled punctures in one step into the left auricle and left ventricle through a fine flexible needle is technically easier and safer than the use of Bjork's catheterization (trochar into the left auricle and sound into the left ventricle). The authors believe that the procedure is of value in determining the presence of mitral regurgitation in cases which appear to be pure mitral stenosis clinically. Pressure tracings of the C wave give indication of the suppleness of the mitral valve where there is leakage, and, finally, the procedure can be of value in diagnosis in certain situations (apex murmur in an old rheumatic patient) or where surgical indications are difficult (aortic stenosis).

Polymyxin Treatment of Infantile Diarrhea Due to E. Coli Resistant to Other Antibiotics.—Polymyxin by mouth, and in some cases by injection, was used in an epidemic

where other antibiotics were found clinically and by sensitivity tests to be of no value. After treatment for 8 to 10 days the stool cultures became negative for pathogenic E. coli in 8 to 15 days. Renal function was followed closely, but no serious signs of toxicity were found.

Acute Eczema Due to Mercury Sensitivity.—Two cases of sensitivity to Mercurochrome are reported, in both of which episodes of acute eczema also followed visits to country fairs with shooting galleries; mercury vapor liberated by the exploding rifle cartridges was believed responsible, and skin tests confirmed the mercury sensitivity.

Remissions in Acute Leukemia.—Long remissions in acute leukemia are very uncommon; therefore the authors report the case of a 17-year-old girl treated by transfusions, steroids, Aminopterin, and antibiotics who had a clinical and hematological remission lasting three years and three months, followed by a sudden and fatal relapse.

Danger of Hyperimmune Serum in the Treatment of Pertussis.—In 1951, Debre et al. reported 555 cases of pertussis treated with hyperimmune serum, with 7 deaths, which in view of the seriousness of the infection, could not be said to be due to the serum. However, the clinical impression remains that use of hyperimmune serum in gravely ill infants can be followed by serious and even fatal reactions, comprising a sudden hyperthermia a few hours after the injection, with prostration, coma, and death within 24 hours to 3 days after the first injection.

Radiology, Syracuse, N. Y.

Abstracted by William E. Anspach, M.D.

69 (Nov.) 1957

* Agenesis of Lumbo-Sacral Vertebrae: A Report of Two Cases in Living Infants. Everett L. Pirkey and Jack H. Purchell.—p. 726.

Agenesis of Lumbo-Sacral Vertebrae: A Report of Two Cases in Living Infants.—Complete absence of the lumbosacral vertebrae indicated that developmental arrest occurred about the 10th fetal week. Rotund masses of osseous tissue, instead of the lumbar and sacral vertebrae, represented morphologic dysplasia after histogenesis in the osseous tissue had started. Presumably the factors responsible for such changes had their effect much later in fetal life.

Possible etiological factors are syphilis, poor nutrition, intrauterine inflammation, heredity, endocrine disorders, and severe illness, but no extrinsic factor could be found in the authors' case. They were unable to find a report of a similar case in the radiological literature.

News and Comment

ANNOUNCEMENTS

Course in Neuromuscular Diseases of Children.—The Cook County Graduate School of Medicine announces a two-week intensive course in neuromuscular diseases of children, with special emphasis on cerebral palsy, to be given by Dr. Meyer A. Perlstein for the period of July 7 to 18. This is an intensive didactic and clinical course designed for pediatricians, orthopedists, neurologists, psychiatrists, and physiatrists interested in the care and treatment of children with neuromuscular handicaps. Emphasis will be placed on the practical clinical aspects of treatment and rehabilitation procedures. The course will include trips to demonstration clinics and treatment centers. The fee for the course, which is $250, will include the cost of transportation and accommodations during the field trips. Registration in the course is limited. For further information, write to John W. Neal, Registrar, Cook County Graduate School of Medicine, 707 S. Wood St., Chicago.

Service of Orientation and Information.—The International Children's Center of Paris announces a new Service of Orientation and Information, designed to aid pediatricians and social workers on professional trips to other countries. It will supply information to research workers on libraries and study resources, arrange introductions or visits to institutions and laboratories, and make whatever contacts are desired.

Prof. Henri Bonnet, who is in charge of the Service, will be in his office every Monday and Friday afternoon and Thursday morning. The address is International Children's Center, Chateau de Longchamp, Bois de Boulogne, Paris 16, France. In his absence, his secretaries will supply information and make appointments. Free service to the Center is provided from the Place de l'Etoile. The telephone number is LONgchamp 26-62, 13-97.

Residency in Pediatric Allergy.—Childrens Hospital, Columbus, Ohio, affiliated with The Ohio State University College of Medicine, offers a one-year residency in pediatric allergy to candidates with two years' accredited residency in pediatrics. Address correspondence to John H. Mitchell, M.D., Division of Allergy, The Ohio State University, Columbus, Ohio.

Fellowship for Study of Handicapped Children.—A fellowship program, to start July 1, 1958, for training in the broad area of handicapped children is being sponsored by the Hospital School for Severely Handicapped Children and the Child Development Clinic of the Department of Pediatrics at the State University of Iowa, Iowa City.

The Hospital School has a residential program for 60 severely physically handicapped children considered to be educable and also conducts an outpatient program. All types of physical handicaps are considered but especially cerebral palsy. The Child Development Clinic is concerned about all aspects of deviant development in children, especially mental retardation. It has both inpatient and outpatient functions. Both the Hospital School and the Child Development Clinic operate in conjunction with the Department of Pediatrics.

Duties would be directed toward being intimately concerned with the children in the inpatient groups and also helping with outpatient evaluations. Ample opportunity would be provided to do investigative work in this area, the exact nature of which would be directed by the person's interests. Attending certain national or regional meetings and attending certain postgraduate courses would be a part of the fellowship program.

An appointment of Instructor in the Department of Pediatrics will be offered. The salary will be $4000 to $5000, depending on qualifications. Applications can be made to either Dr. Raymond R. Rembolt or Dr. Robert B. Kugel, Department of Pediatrics, University Hospitals, Iowa City.

Books

BOOKS RECEIVED

Pharmacologic Principles of Medical Practice. By Krantz and Carr. Price, $14. Pp. 1311, with illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1958.

Psychoanalytic Study of the Child, Vol. XII. Edited by R. S. Eissler et al. Price, $8.50. Pp. 417. International Universities Press, Inc., 227 W. 13th St., New York 11, 1958.

Drugs, Their Nature, Action and Use. By Beckman. Price, not given. Pp. 728, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1958.

BOOK REVIEWS

Erythroblastosis Fetalis Including Exchange Transfusion Technic. By Fred H. Allen Jr., M.D., and Louis K. Diamond, M.D. Price, $4.00. Pp. 143. Little, Brown & Company, 34 Beacon St., Boston 6, 1958.

The best way to review this excellent book is to reproduce the Foreword, by Dr. Edith L. Potter, as follows:

"It is a rare and intensely satisfying experience to find a book that is exactly what you would like to have been able to produce yourself. No matter how well someone else's manuscript is written there are almost always parts with which you disagree or which you think you might have done better, but in this one I found myself invariably agreeing and admiring.

"Dr. Diamond and Dr. Allen have accomplished a remarkable feat. They have taken a complicated subject with a voluminous literature and have managed to give the reader in relatively few pages a clear, unbiased picture of the current status of erythroblastosis and the blood factors by which it is caused. They are well fitted for this task because of their long interest and experience in the subject. Dr. Diamond was an authority on the clinical aspects of erythroblastosis long before its cause was discovered. He is a personal friend of most of the people working in this field and through reading and discussion has been constantly aware of all thought on the subject and of all investigations being carried on. His clinical experience at the Boston Lying-in Hospital, at the Children's Hospital and with the newborn services of nearby hospitals to which he is consultant has been unparalleled anywhere else in the world.

"Dr. Diamond and Dr. Allen have made many contributions to our knowledge of erythroblastosis and to them, more than any except those who first discovered the existence of Rh, innumerable children owe their lives. They have been largely responsible for the moderately recent change in philosophy concerning the treatment of erythroblastosis. For many years treatment was aimed at combating anemia. Now it is recognized that the danger to the infant lies in prolonged exposure of its brain to high levels of bilirubin and that severe anemia can be tolerated without harmful effect. Multiple exchange transfusions of compatible blood as a means of preventing excessive bilirubinemia has been established by them as the only satisfactory method of treatment.

"Since more physicians have become more aware of the problems posed by maternal immunization there seems to have been somewhat less tendency to consult a specialist when considering the treatment of an infant, and in some instances infants have suffered from delay in being admitted to a hospital for treatment. Prompt treatment of a severely affected infant is often essential for survival, and even in the case of a mildly affected infant it is easier to prevent a rise in bilirubin than it is to bring it down after it has once become greatly elevated. The authors caution, and very rightly so, against being misled by hemoglobin levels and stress the importance of early jaundice and increasing bilirubinemia as indications for exchange transfusion even though the hemoglobin remains moderately high.

"Dr. Diamond and Dr. Allen have written many papers on various phases of Rh and erythroblastosis. These and their more current observations are summarized in the present

book and are viewed in relation to the experiences of other workers in the field. The material is well organized and is presented in a logical, clear, and simple style. All the things you want to know are there—facts and opinions and the basis for them. This is medical writing as it should be, by people who know the subject thoroughly and how to present it so that the reader will know too."

Rheumatic Diseases, Rheumatism and Arthritis. By Heinrich G. Brugsch. Price, $10.00. Pp. 330, with 58 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1957.

This book is based largely upon the personal experience of the author at the arthritis clinic of the Boston Dispensary. It is written from the internist's point of view, but pediatricians will find it to be a good guide. Emphasis is upon clinical observations and therapy. The approach is practical, and the coverage, comprehensive. It will not serve as a source of detailed information, but there are well-chosen lists of references at the end of each chapter.

In some areas the recommendations are not current. For example, on page 80 penicillin is listed categorically as the most effective drug in staphylococcal infections. Erythromycin and novobiocin are not mentioned. Chlortetracycline is stated to be of value in typhoid fever, but chloramphenicol is not mentioned. For the treatment of tuberculosis, a combination of streptomycin and aminosalycilic acid is recommended, but isoniazid is not included.

There are a number of pertinent illustrations, but the quality of the reproductions is only fair.

The chapters on rheumatoid arthritis and gout are particularly well done.

B. M. KAGAN, M.D.

Pica. By Marcia Cooper. Price, $3.75. Pp. 114. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

This book deals with the habit of eating clay, plaster, charcoal, or other unusual things. The author's hypothesis is "that poor nutrition may be the underlying factor in pica," and she tries to document her point by a historical review reaching back many centuries, from reports of colonial physicians on the habits of plantation workers and from earlier European and American authors.

The behavior of domestic animals and the self-regulatory functions as observed in studies of laboratory animals and young children as well as some (although meager) recent studies also support her thesis. A study conducted in Baltimore in which the author participated also indicates that pica is related to nutritional factors (feeding problems) and illness and physical defects but not to intelligence, other behavior problems, birth weight, age of weaning, or family income.

An analysis of edible earths indicates that they may contribute to nutrition by the effect of pH, by supplying iron and potassium, and by playing a part in the synthesis of B vitamins.

The value of this book lies essentially in the compilation of the literature (102 references are cited) and in its suggestion for further research in the field. I was not entirely convinced that the examples cited necessarily supported the aut' or's views: For instance, the historical sources quoted to demonstrate the nutritional causation also stated the need for a "healthy mind in a healthy body" and in the chapter on relation of pica to nutrition behavioral factors and habit disturbances play an important role. This, incidentally, corresponds to the findings in the chapter "Relation of Pica to other Behavior Problems," which in itself may not be statistically significant but still shows that "the average number of problems in the pica group as a whole is larger than in the non-pica."

Although the controversial question of etiology may not be settled by this book, it should be of value to any pediatrician "reading up" on the subject and an excellent source of reference for any student in the field.

KURT GLASER, M.D.

The Physiology and Biochemistry of Lactation. By S. J. Folley. Price, not given. Pp. 153. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

This book presents a critical and authoritative review of present knowledge of the complex physiological and biochemical processes involved in the growth and function of the mammary gland. The material is presented in a logical and interesting manner, and there is a complete list of references and an index of authors and subjects.

Although there is little mention of the human mammary gland, many of the mammalian studies are thought-provoking to a person interested in human breast feeding. The first three chapters are devoted largely to the endocrine and neuroendocrine control of lactation. The fourth chapter on physiology should be of special interest to those who teach mothers to breast feed. In the last two chapters a thorough account is given of the synthesis of fat, lactose, and protein in the mammary gland.

THOMAS H. SHEPARD, M.D.

Six Children. By Estelle J. Foote. Price, $5.50. Pp. 317. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1956.

The author, psychiatrist in charge of a traveling school clinic, bases her book on her nine years of experience with more than 3600 children. Although she intended the book for physicians, school personnel, and "all who work with children in diagnostic and treatment clinics," I gained the impression that the writing is too simplified for the physician, but, because of its instructive, clear form, not mystified by highly technical terms, it can be of great value to "teachers, supervisors, principals and superintendents of schools." It is for this group that the book seems basically intended.

For all those working in clinics the book has a very useful appendix of forms and charts which demonstrate the meticulous work of the author and can be handy for clinics doing similar work. They are precise, and their explanations are clear; consequently they can be used without difficulty by persons who are not psychiatrically trained.

The book deals with six categories into which the author was able to fit most of the children she studied: the child with high intelligence, the child with low intelligence, the brain-injured child, the emotionally maladjusted child, the child of unusual cultural background, and the child of unusual training. Each of these types is described under the headings of history (family, personal, developmental, and the child's characteristics), the school history and test results, psychometric evaluation, physical examination, and psychiatric evaluation. Several case reports illustrate each type. Most space is allotted to the "slow thinking child," which constituted the largest number of referrals to the author's clinic.

Apart from the six groups, the author discusses all too briefly the child with a physical handicap and the child called delinquent. This is regrettable, since by number as well as importance they deserve a more detailed treatment in a book which is intended to serve those concerned with the care of children, especially in the school setting.

I believe that the book is of greatest value for school personnel and for those who wish to utilize the well-thought-through "Forms and Charts," to which about one fourth of the volume is devoted.

KURT GLASER, M.D.

Therapeutic Heat. By 23 contributors and edited by Sidney Licht. Price, $12.00. Pp. 466, including appendix and indices. Elizabeth Licht, New Haven, Conn., 1958.

Rehabilitation medicine has, in the past fifteen years, made notable advances, mainly as a result of the increasing incidence of chronic diseases and disabilities in all age ranges. Techniques utilized in its practice have, of necessity, been largely empirically derived, but, despite this, rehabilitation is now well established as an important component of contemporary medical care. There is a great need, however, for employment of the scientific method and objective analysis for the procedures utilized in its practice. Therefore, the appearance of the second volume in the Physical Medicine Library is doubly welcome, since it undertakes a thorough analysis of probably one of the widest physical therapeutic agents used in medicine—heat.

Twenty-three American and European contributors with diverse experience have created a scholarly discourse, encompassing basic physics, physiology, therapeutics, instrumentation, and clinical applications in a variety of syndromes. Each of the authors is expert, thorough, and critical and presents his material in the best tradition of scientific writing.

The irregularities caused by varying styles usually encountered in compendia have been overcome by obviously excellent editorial effort, and the material reads smoothly and logically. In the sections on clinical applications, however, there is some degree of overlap and divergence of opinion.

Clinical entities considered are rheumatic diseases, orthopedics, vascular and neuromuscular disorders, diseases of the pelvis, and diseases of the eye.

There are excellent bibliographies for each chapter, a wealth of clear illustrations and diagrams, and carefully developed subject and author indices. Of special interest to practitioners is a section on legal implications. There is, in addition, a comprehensive survey of the status of ultrasound therapy.

The volume is attractive, although the price of $12.00 seems slightly high for a volume of this size.

The book is a much needed addition to the literature, both basic and clinical, in the increasingly important field of physical medicine and rehabilitation and is recommended for physicists, physiologists, medical students, general practitioners, and specialists.

JOSEPH G. BENTON

Treatment of the Child in Emotional Conflict. By Hyman S. Lippman. Price, $6.00. Pp. 298. McGraw-Hill Book Company, Inc., 330 West 42d St., New York 36, 1956.

This book presents a clear picture of the way in which a psychoanalytically oriented child-guidance clinic operates, and makes clear the understanding and rationale by which the staff tries to understand the child and formulate a plan of treatment. The author was originally a practicing pediatrician who, after training in child psychiatry and child analysis, has been Director of the Amherst H. Wilder Child Guidance Clinic, in St. Paul, Minn., for the past twenty-five years.

It contains excellent sections on various childhood neuroses, personality or character problems, acting out or antisocial behavior, and the psychotic and brain-damaged child. In the section on neuroses there is a chapter on the child with a depression. This relatively common, but often unrecognized, problem deserves more attention. It is unfortunate that the author has not included more discussion of the physiological disturbances which often accompany this condition.

There is an excellent statement on the qualifications of a therapist which includes the following: "Free from . . . serious emotional conflict, since he must be able to react objectively to all kinds of symptoms and behavior in children and their parents; . . . should be able to love children and accept their love, but must not depend on the love of children he serves. . . . He must be secure . . ." and "feel strong enough to be firm when . . . necessary." These qualities are equally desirable in any doctor caring for children. Perhaps some day pediatric departments will consider the development of these qualities as essential as the knowledge of acid-base balance.

Although, as is usually the case with any book in this area, the pediatrician will feel frustrated that specific advice and techniques are not given, he will find his understanding considerably broadened. One hopes that he will be able to use this increased understanding with the children and families who constitute his practice.

SHERMAN LITTLE, M.D.

Microscopic Anatomy of the Temporal Bone. By Dorothy Wolff, A.A., M.A., Ph.D.; R. J. Belluci, B.S., M.S., M.D., and A. A. Eggston, B.S., M.D. Price, not given. Pp. 414. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1957.

This is a splendidly prepared book and should prove invaluable to the student of otology, which of course should include anyone purporting to practice this specialty.

The volume fills a long-felt need, as material on the microscopic anatomy of the temporal bone has been scattered in fragments among various journals.

Study of these pictured sections should give the otologic surgeon the three-dimensional concept of the temporal bone necessary not only for the performance of operations to restore function but also for the older procedures of draining of suppuration in the petrous pyramid if these should again prove necessary.

The text is clear, terse, and informative; the reproductions of microscopic sections are excellent, and the book has an important but sometimes neglected addition, a good index.

HENRY L. WILLIAMS, M.D.

Hormones in Blood: Ciba Foundation Colloquia on Endocrinology, Vol. XI. Edited by G. E. W. Wolstenholme and E. C. P. Millar. Price, not given. Little, Brown & Company, 34 Beacon St., Boston 6, 1957.

This volume contains detailed discussions of several of the most recent advances in the study of endocrine physiology by the persons largely responsible for these advances. For

example, the present status of the question of assay for antidiuretic hormone in the blood is discussed by Dr. H. Heller, who has been a prime mover in this field of investigation for many years. Thyroid hormones in the blood are discussed by Dr. R. Pitt-Rivers, and corticotropin in the blood, by Dr. G. Sayers. Other topics covered are the blood levels of thyrotropic hormone, insulin, steroid hormones, aldosterone, and catechol hormones in various experimental conditions. An interesting discussion is also presented of the metabolism and placental transmission of hydrocortisone (Cortisol) during pregnancy near term.

The volume represents an accumulation of many of the most important recent advances in the field of endocrine physiology. It will be invaluable to those whose research is concerned with this field.

S. A. KAPLAN, M.D.

IF YOU CHANGE ADDRESS

Please notify us at least six weeks before you make the change.

With your notification, include the address label clipped from the latest copy of the journal. If your city has postal zone numbers, be sure to include the zone number in your new address.

You will want to get your copies promptly; so notify us at least six weeks in advance. Send your change notice to

A. M. A. Journal of Diseases of Children
American Medical Association
535 North Dearborn St.
Chicago 10, Illinois

For

CONSTIPATED BABIES AND CHILDREN

laxative modifier of milk—
promotes aciduric intestinal flora

Malt Soup Extract promotes growth of favorable aciduric intestinal flora and provides mild peristaltic stimulation. Safe, effective, non-habit forming—as confirmed by medical literature and clinical use for over 45 years.

NOW 2 FORMS

* Specially processed non-diastatic barley malt extract neutralized with potassium carbonate.

LIQUID:
In 8 oz. and Pt. jars.

POWDER:
In 8 oz. and 16 oz. jars.
(use heaping measure)

FOR INFANTS: A gentle laxative modifier of milk. Just add one or two tablespoonfuls routinely to the day's formula, or in water for breast-fed infants. Prompt results, even in stubborn cases.

FOR CHILDREN: One or two tablespoonfuls with breakfast and at bedtime, by spoon or in milk. Makes a delicious "malted" drink.

SEND FOR SAMPLES **BORCHERDT CO.** 217 N. WOLCOTT AVE., CHICAGO 12, ILL.

MALT SOUP EXTRACT

Of interest to you

and your patients

THE MENACE OF ALLERGIES

WHAT WE KNOW ABOUT ALLERGY
by Louis Tuft, 12 pages, 15 cents

FOOD ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

SKIN ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

ASTHMA AND HAY FEVER
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10 • ILLINOIS

rapid screening test for

CYSTIC FIBROSIS

Silver Chromate Agar in disposable plastic petri dish, sealed in polyethylene bag.

Patient's finger, hand, toe or foot is applied to plate surface. Excess chloride in sweat, a diagnostic sign of cystic fibrosis, causes immediate, clear-cut color change.

$1 per plate—unit package, 3 plates.
May be conveniently stored, ready for instant use.

Hyland Laboratories Hyland

4501 Colorado Blvd., Los Angeles 39, Calif.
252 Hawthorne Ave., Yonkers, N.Y.

PRESCRIPTION SERVICE FOR

ENURESIS

NOT sold or advertised to the public. NOT available without your Rx. S. & L. ENURESIS ALARMS can be rented ONLY by patients for whom you prescribe. The alarm is used in the patient's home, under your supervision.

Professional supervision is important, but simple. A reprint from **The Journal of the A.M.A.**, describing this therapy in detail, will be enclosed with our reply to your inquiry.

Our EXCLUSIVELY PROFESSIONAL service, inaugurated in 1947, is available throughout the U. S. You need only validate our business reply order form and give it to the patient. We notify you when the patient orders an alarm, and again when it is returned.

- PROFESSIONAL QUALITY APPARATUS
- LOWEST COST, $5 PER WEEK
- CONVENIENT SERVICE
- OVER 90% EFFECTIVE
- ETHICAL

Write for Rx Forms and Brochures

S. & L. SIGNAL COMPANY, INC.
525 HOLLY AVENUE MADISON 5, WIS.

Viokase Pancreatin 4 times the N.F. X minimum potency standards.

VIOKASE

CONFORMS TO

WHOLE PANCREAS
Not an extract!

PHYSICIANS' COUNCIL ON CHILD NUTRITION

EFFECTIVE substitution therapy in demonstrated pancreatic deficiency.

CODE FOR ADVERTISING

NOT ENTERIC COATED

Shwachman, H., The Child in Health and Disease, Grulee and Eley, 2nd Edit.

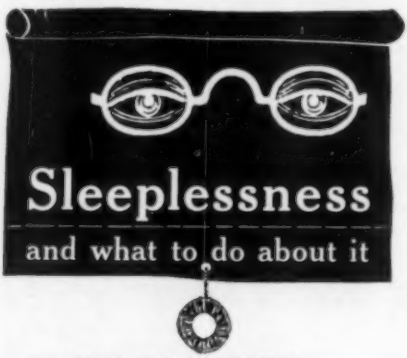
Shwachman, H. and Leubner, H., Advances in Pediatrics, VII, 249, 1955.

Kagan, B. M., Illinois Medical Journal, 107, 120, 1955.

Kumar, B. B., and Gibbs, G. E. A.M.A. Journal Diseases of Children, 91:606, 1956.

Literature on request.

VIOBIN, Monticello, Illinois

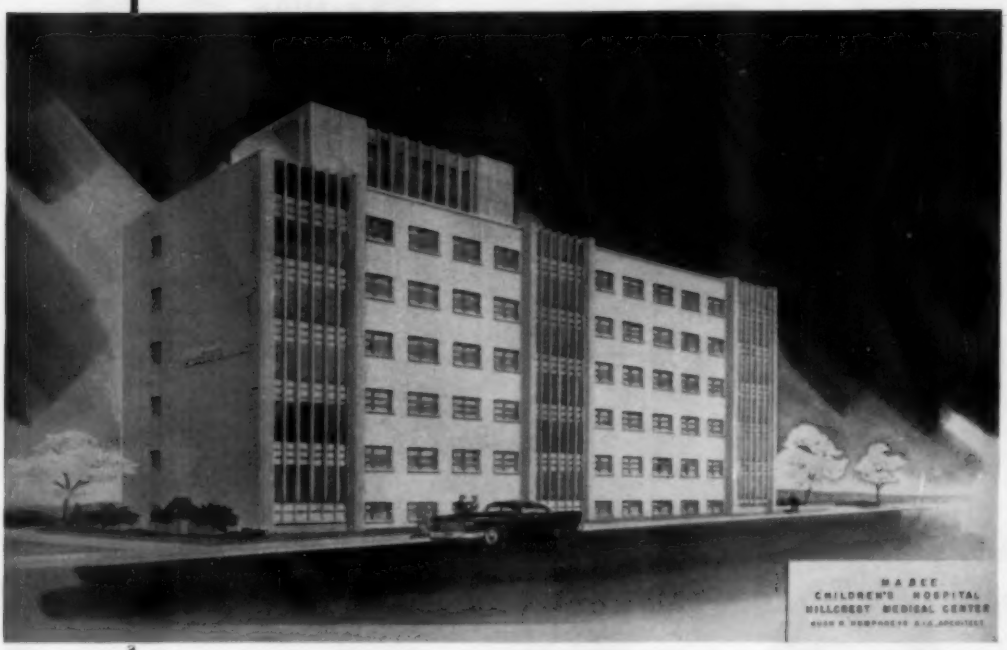


SO YOU CAN'T SLEEP?
by P. H. Fluck
8 pages, 15 cents

SLEEPLESSNESS AND WHAT TO DO ABOUT IT by Donald A. Laird, Ph.D.
8 pages, 15 cents

ROADS TO RELAXATION
by Joseph L. Fetterman, M.D.
4 pages, 10 cents

AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St., Chicago 10, Illinois



Through the benevolence of one of our philanthropists in Tulsa, Hillcrest Medical Center is building an ultra-modern, 135 bed Children's Hospital. We are also building a 200 bed addition for general patients, bringing our total bed capacity to between 700 and 800 beds.

Tulsa is one of the most modern cities in America and a good place to live.

We need some residents in pediatrics. Anyone interested please apply to the House Staff Committee at Hillcrest Medical Center, 1653 East 12th Street, Tulsa, Oklahoma.

little

How to win friends ...

The Aspirin that Tastes So Good.

The Flavor Remains Stable down to the last tablet.

25¢ Bottle of 48 tablets (1¼ grs. each).

We will be pleased to send samples on request.

THE BAYER COMPANY DIVISION

of Sterling Drug Inc.

1450 Broadway, New York 18, N. Y.

air
in
a
hurry

\+

protection
from asthma
for hours
with 1
convenient tablet—

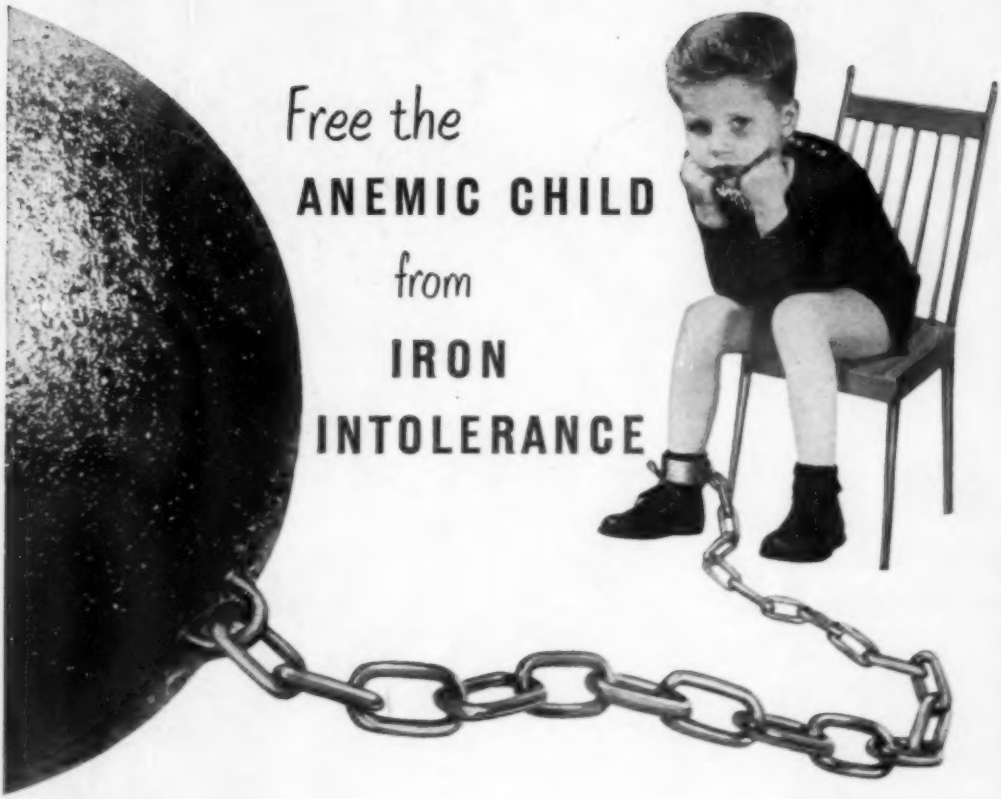
Nephenalin®
PEDIATRIC

each tablet contains:

Aludrine (Isoproterenol HCl)	5 mg. (in coating)
plus	
Theophylline	100 mg. (1½ gr.)
Ephedrine sulfate	12 mg. (⅜ gr.)
Phenobarbital	8 mg. (⅛ gr.)

dose: Keep under tongue 5 minutes for rapid asthma relief; then swallow. Not more than 1 tablet in 4 hours, or 5 tablets per day. Bottles of 20 and 100.

Thos. Leeming & Co. Inc. New York 17, N. Y.



Free the ANEMIC CHILD from IRON INTOLERANCE

℞

FERGON®

BRAND OF FERROUS GLUCONATE

HIGH HEMOGLOBIN RESPONSE

EXCELLENT TOLERANCE

FOR ALL SIMPLE IRON DEFICIENCY ANEMIAS

Children: 5 to 15 grains (1 to 3 tablets of 5 grains or 1 to 4 teaspoonfuls of elixir) daily.

Infants: 30 drops of elixir, gradually increased to 1 teaspoonful, daily.

Winthrop LABORATORIES NEW YORK 18, N. Y.

SUPPLIED: **Fergon tablets of 5 grains,** bottles of 100 and 500.
Fergon tablets of 2½ grains, bottles of 100.
Fergon elixir 6% (5 grains per teaspoonful), bottles of 16 fl. oz.

Fergon, trademark reg. U.S. Pat. Off.